
بهترین نرم افزار مطب
مالی و نسخ الکترونیک
اکسیر

The Fetus and the Neonatal Infant

PART X

Chapter 114

Overview of Morbidity and Mortality

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INFANT MORTALITY

The **infant mortality rate** is a metric used by public health agencies, policymakers, and governments to gauge the overall quality of pediatric and population health among a given population residing within geographically defined boundaries. The rate is stated as the number of infant deaths per 1,000 live births. In the United States, an *infant death* is defined as mortality taking place from the time after delivery at any gestational age, up to the first birthday. No age correction is made to account for a premature birth. Each infant death is assigned to a geographic entity (e.g., county, state, country) based on the birth parent's home address at the time of death (Fig. 114.1). The definition of a *live birth* is typically based on the complete expulsion of the productions of conception from the uterus and one of three criteria: detection of cardiac activity (by auscultation or palpation of the umbilical cord stump), definite movement generated by voluntary muscle contraction, or any respiratory effort. It is important to note that this definition does not incorporate any gestational age cutoff. The risk of mortality and major morbidity is particularly high around the time of birth (Fig. 114.2). Therefore, within the spectrum of infant mortality, certain subcategories are used in maternal and child health practice to focus on specific periods of high risk. The **perinatal period** is typically defined as the time from the 28th week of pregnancy through the 7th postpartum day. The **neonatal period** spans the first 28 days of life and can be further subdivided into *early neonatal* (first 7 days) and *late neonatal* (days 8-28) periods (Fig. 114.3). The **post neonatal period** covers the time after the first 28 days and until the first birthday. The primary causes of mortality shift as infancy progresses, such as during the perinatal and neonatal periods and preterm birth (Figs. 114.4 and 114.5), and when congenital malformations predominate (see Fig. 114.3; Fig. 114.6), whereas unsafe sleep practices, infections, residual effects of prematurity, and congenital malformations account for most deaths during the remainder of infancy. In developing countries with limited resources, preterm birth remains a concern, but other causes, such as infection, birth asphyxia, and complications of labor and delivery, add an additional burden.

Rankings and Trends

Over the past century, neonatal and infant mortality rates have declined in the United States and across most of the world. However, rates continue to differ worldwide (Fig. 114.7). In general, the highest rates are observed in low-resource, developing countries. However,

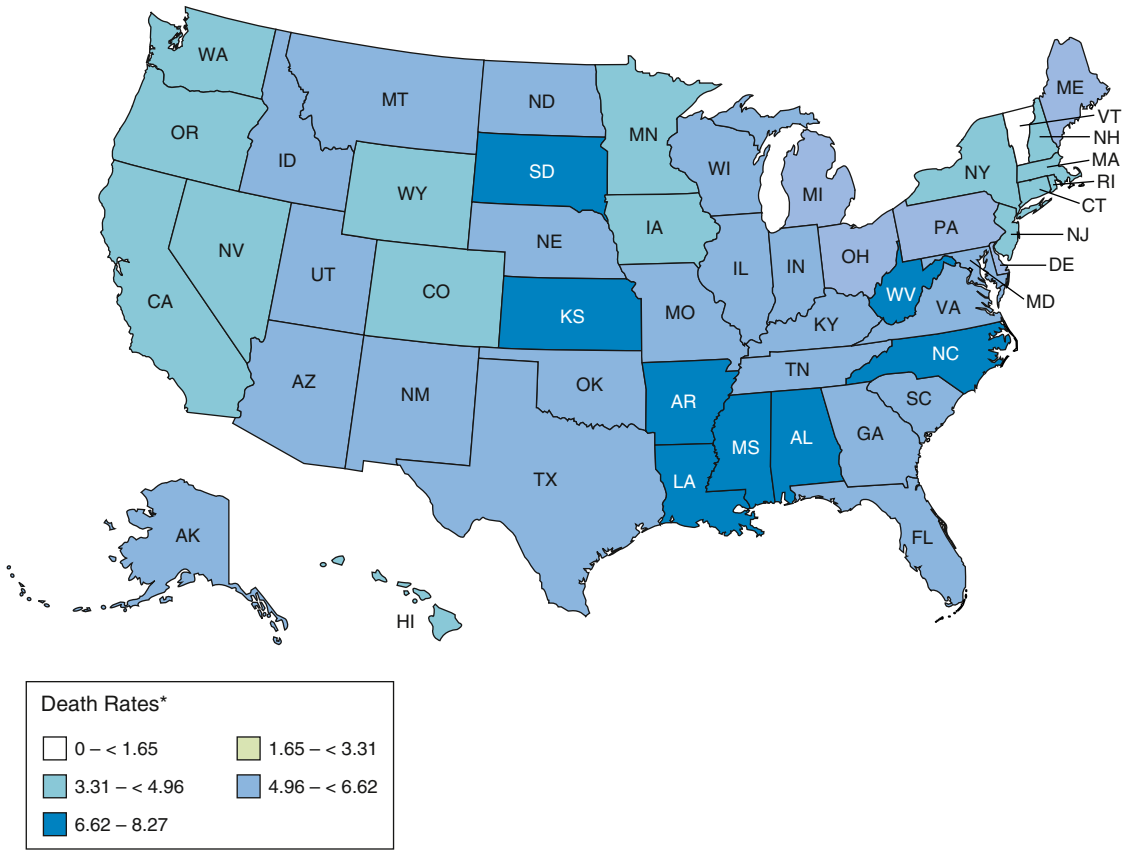

Fig. 114.1 Infant mortality rates by state, 2020. *The number of infant deaths per 1,000 live births. (*From CDC National Center for Health Statistics. https://www.cdc.gov/nchs/pressroom/sosmap/infant_mortality_rates/infant_mortality.htm*)

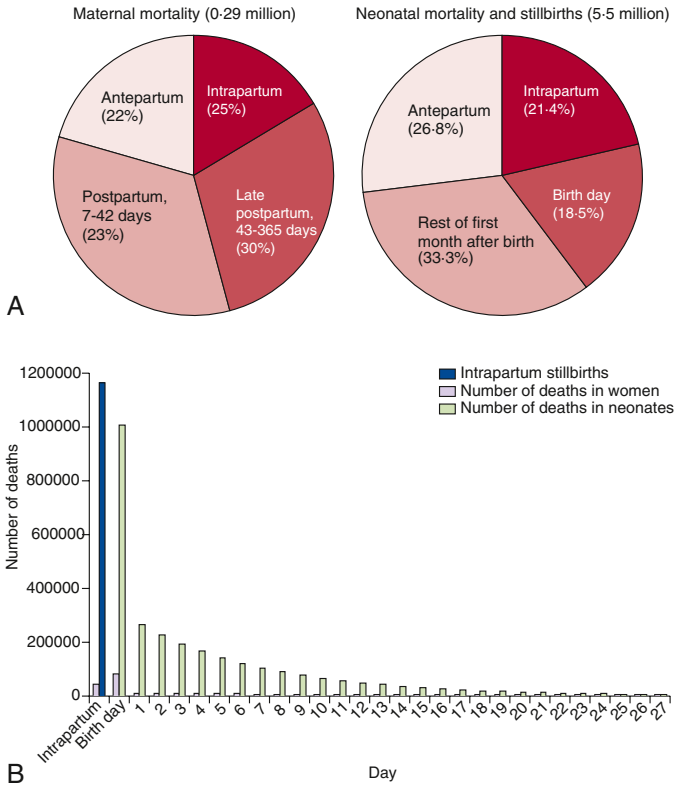

Fig. 114.2 A, Timing of death for women and birthing people in the first year of life (i.e., maternal mortality) and for fetuses and babies from 28 weeks' gestation up to 28 days of life (i.e., perinatal and neonatal mortality). B, Number of deaths during labor and the first month after birth of women and their babies (intrapartum stillbirths and neonates). Insufficient data were available to accurately assign the day of death for the 1.4 million antepartum stillbirths and 63,000 maternal deaths occurring during the last trimester of pregnancy (before the onset of labor). (*From Lawn JE, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384:189–202. Fig. 5; updated data in A from https://www.cdc.gov/reproductivehealth/maternal-mortality/erase-mm/data-mmrc.html#print.*)

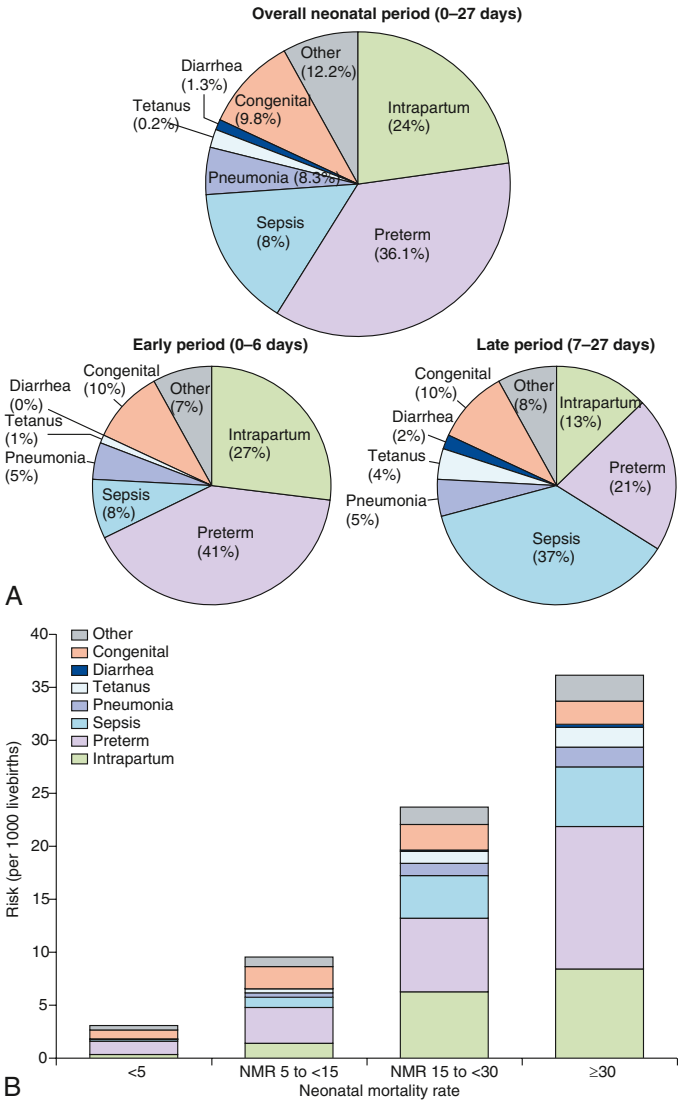

Fig. 114.3 A, Cause of death distribution for the neonatal period, and by the early (<7 days) and late (7-28 days) neonatal periods, for 194 countries in 2012. B, Variation in cause-specific neonatal mortality rates (NMRs) by level of NMR in 2012, showing risk difference by cause of death compared with the lowest mortality group (NMR <5). Data from Child Health Epidemiology Reference Group and World Health Organization (WHO) estimates for 194 countries for 2012. Estimates are based on multicause statistical models. In 2012, an additional estimated 196,000 deaths occurred in the post neonatal period from neonatal conditions (preterm birth, intrapartum related) and an estimated further 309,000 from term, small for gestational age. (*From Lawn JE, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384:189–202. Fig. 6; data in A from Perin J et al. Global, regional, and national causes of under-5 mortality in 2000-19: an updated systematic analysis with implications for the Sustainable Development Goals. The Lancet Child & Adolescent Health 2022; 6:106-15. Derived from Figure 1. https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00311-4/fulltext.*)

the United States remains an anomaly among nations in the developed world. Table 114.1 shows infant mortality rates from a representative sample of developed countries. The rates are adjusted to exclude deaths before 24 weeks' gestation to account for potential variation in definitions of live births that might occur at the threshold of viability and to ensure comparability. Beginning in the 1980s, U.S. rates began to consistently exceed other developed nations. Since 2010, U.S. infant mortality rates have consistently been approximately 75% higher than the average developed country. A wide range of infant mortality rates is also observed within the United States, with the highest rates in the Southeast and lowest rates in the Upper Midwest, the Northeast, and the West Coast (see Fig. 114.1).

MAJOR CAUSES OF INFANT DEATH

In the United States and Europe, most infant deaths fall into one of three major categories of causation: congenital malformations, low birthweight (LBW)/short gestation, and maternal complications (see Fig. 114.6). When cause of death is classified using the *International Classification of Diseases, Tenth Revision,* classification system, congenital malformations are the leading cause, followed by disorders related to prematurity and LBW. However, globally, preterm birth rather than congenital malformations accounts for the majority of deaths for all children under 5, when deaths from unique complications of prematurity are included. Sudden unexpected infant deaths (SUIDs) account for the fourth most common cause of infant mortality, a category of sleep-related events that includes sudden infant death syndrome (SIDS) and unintentional injuries such as due to accidental suffocation and strangulation in bed. Infections, trauma, birth asphyxia, and injuries account for the remainder of infant mortality cases in the United States. The pattern differs in the developing world, where infections and asphyxia predominate. The U.S. **preterm birth rate** is substantially higher than in other developed countries and best explains elevated U.S. infant mortality rates. Worldwide, preterm birth rates display a tight concordance with infant mortality rates, providing further evidence for the importance of this linkage (see Fig. 114.5). In the era of modern neonatal intensive care, most preterm birth deaths occur among the earliest gestational ages (<28 weeks), and within the first

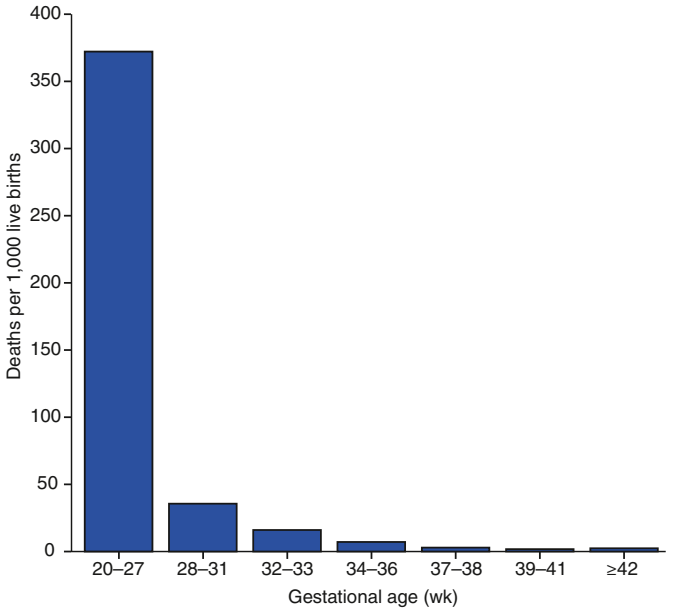

Fig. 114.4 Infant mortality rates by gestational age—United States, 2013. Deaths in children age <12 mo per 1,000 live births. (*From Shapiro-Mendoza CK, Barfield WD, Henderson Z, et al. CDC Grand Rounds: Public health strategies to prevent preterm birth. MMWR. 2016;65[32]:826–830; updated data from Ely DM,Driscoll AK. Infant mortality in the United States, 2020: data from the period linked birth/infant death file. National Vital Statistics Report. Centers for Disease Control and Prevention. 2022;71(5):1-18. https://www.cdc.gov/nchs/data/nvsr/nvsr71/nvsr71-05.pdf*)

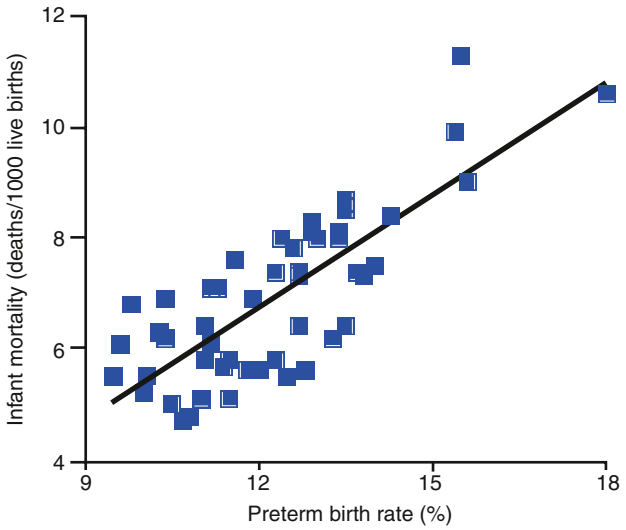

Fig. 114.5 Preterm birth as a function of infant mortality rates for 40 countries. (*Data courtesy L. Muglia, MD, PhD, Cincinnati Children's Research Foundation.*)

few days of life, because of profound respiratory immaturity and insufficiency. The remaining preterm birth deaths result from morbidities associated with prematurity. Late preterm birth (34-36 weeks' gestation) is not a significant contributor to infant mortality. International variation in live-birth registration practices only partly explain the elevated U.S. infant mortality. Although these technical explanations deserve further investigation, they should not be used to explain the high U.S. infant mortality. In the United States, where live-birth registration practices are consistent, substantial variation in infant mortality and preterm birth rates implies *systemic* rather than technical explanations. For instance, systemic racial and ethnic disparities in perinatal

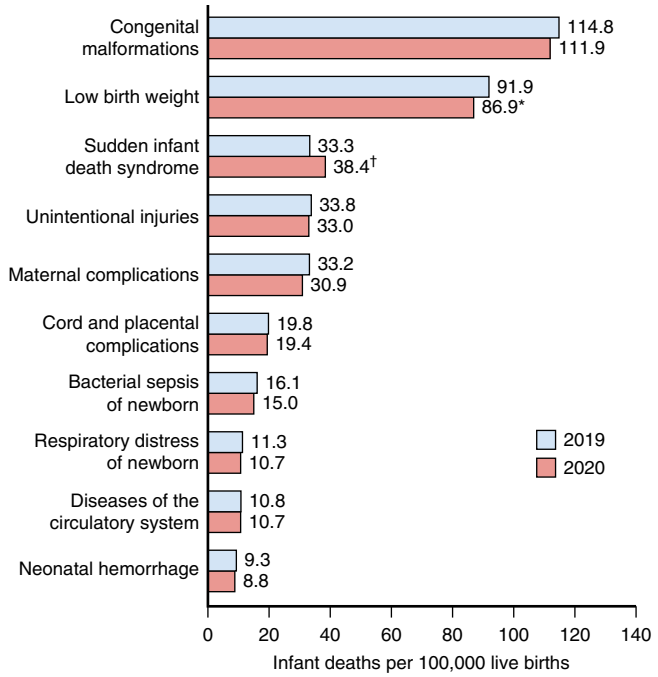

Fig. 114.6 Infant mortality rates for the 10 leading causes of infant death in 2020: United States, 2019 and 2020. *Statistically significant decrease in mortality rate from 2019 to 2020 ($p < .05$). †Statistically significant increase in mortality rate from 2019 to 2020 ($p < .05$). Notes: A total of 19,582 deaths occurred in children under age 1 year in the United States in 2020, with an infant mortality rate of 541.9 infant deaths per 100,000 live births. The 10 leading causes of infant death in 2020 accounted for 67.5% of all infant deaths in the United States. A total of 20,921 infant deaths occurred in 2019, with an infant mortality rate of 558.3 infant deaths per 100,000 live births. Causes of death are ranked according to number of deaths. Rankings for 2019 data are not shown. Data table includes the number of deaths under age 1 year for leading causes of infant death and the percentage of total infant deaths. Access data table at: https://www.cdc.gov/nchs/data/databriefs/db427-tables.pdf#5. (*From Murphy SL, Kochanek KD, Xu J, Arias E. Mortality in the United States, 2020. CDC National Center for Health Statistics. https://www.cdc.gov/nchs/data/databriefs/db427.pdf. Fig. 5.*)

outcomes in the United States are a large contributor to the elevated U.S. infant mortality rates (Fig. 114.8). Multiple gestations (twins, triplets, higher-order plurality) may also contribute to high preterm birth rates (Table 114.2).

Racial and Ethnic Disparities in Infant Mortality and their Drivers

There are significant disparities between infant mortality rates among U.S.-born White infants and those among infants from families of color driven in part by preterm births (see Fig. 114.8). These differences persist even when factors such as insurance, marital status, socioeconomic status (SES) and educational levels are considered. Infant mortality disparities were thought to only affect Black infants; these infants continue to experience infant mortality at rates twice as high as White infants. However, infant mortality disparities have been well documented among American Indian/Alaskan Native and Native Hawaiian/Pacific Islander populations. Despite sharing many of the same risk factors for adverse infant outcomes that Black communities face, the apparent lack of disparities in infant mortality rates and other birth outcomes like preterm birth and LBW among Hispanic/Latinx communities in the United States has been historically termed the *Hispanic birth paradox* or more generally, the *immigrant paradox*. Current data have documented the existence of birth outcome disparities within both Hispanic and Asian communities, when patients are disaggregated by race, country of birth, or immigration-related factors such as length of time in the United States. Black Hispanic infants face higher rates of infant mortality than White Hispanic

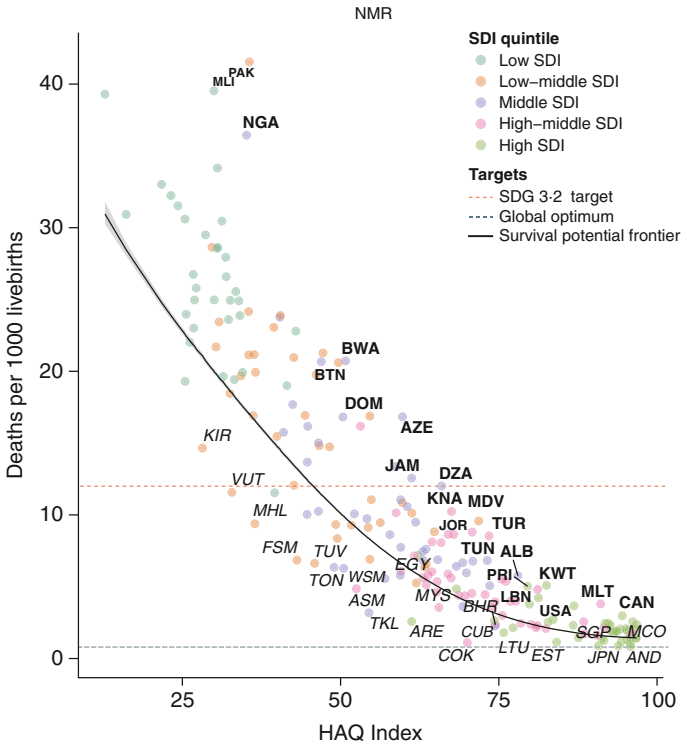

Fig. 114.7 2019 NMR by HAQ Index at the national level. For this, 204 countries were analyzed, and the color of each point indicates the SDI quintile to which that country belongs. HAQ Index ranges from 0 (worst) to 100 (best). The survival potential frontier, global optimum, and SDG targets are indicated as lines on the graph. Gray-shaded bands represent 95% UIs. Countries are labeled with their ISO3 country code in bold when their ratio to the survival potential frontier is in the highest 10% of all countries and in italics when their ratio to the survival potential frontier is in the lowest 10% of all countries. (*Modified from GBD 2019 Under-5 Mortality Collaborators: Global, regional, and national progress towards sustainable development goal 3.2 for neonatal and child health: all-cause and cause-specific mortality findings from the Global Burden of Disease Study 2019. Lancet. 2021;398:870–905. Fig. 4.*)

Table 114.1 Infant Mortality Rate per 1,000 Live Births for Select Developed Countries, 2019

COUNTRY	IMR
Japan	1.8
Finland	2.0
Greece	3.3
United Kingdom	3.7
United States	5.6
Chile	6.0

Data from the World Health Organization Maternal, Newborn, Child & Adolescent Health and Ageing Data Portal: https://www.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/mca/infant-mortality-rate-(per-1000-live-births

infants. Similarly, Southeast Asian/Indian populations in the United States also have elevated infant mortality driven by LBW. Preterm birth and LBW are the key drivers of racial and ethnic infant mortality disparities. The preterm birth rate among non-Hispanic Black infants is much higher than that of other U.S. racial and ethnic groups (see Fig. 114.8), a gap that has persisted for decades. This is especially true for preterm birth rates at very low gestational ages (i.e., <28 weeks) when mortality risks are high, even with the availability of modern neonatal intensive care units (NICUs). Although gaps appear to be narrowing over time for

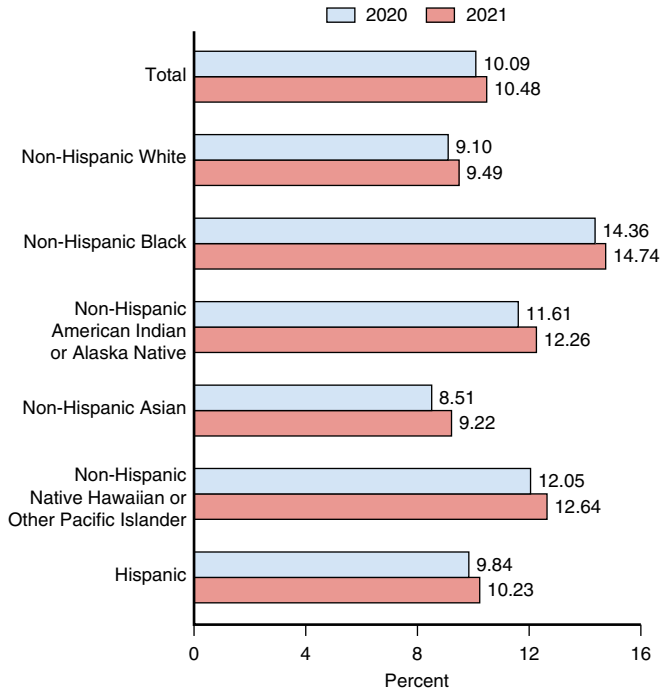

Fig. 114.8 Percentage of preterm births by ethnicity and Hispanic origin: United States, final 2020 and provisional 2021. Note: Preterm is less than 37 weeks' gestation. (*From Hamilton BE, Martin JA, Osterman MJK. Division of Vital Statistics, National Center for Health Statistics: Vital Statistics Rapid Release: Report No. 20, May 2022. Fig. 3. https://www.cdc.gov/nchs/data/vsrr/vsrr020.pdf*)

infants born at <30 weeks' gestation, Black and Hispanic infants experience disparities in morbidity and mortality both while receiving NICU care and after discharge (see Chapter 114.1). Mechanistic explanations for such racial and ethnic disparities remain an area of ongoing research (Table 114.3). Theoretical models focused on individual genetic, health behavior, or socioeconomic differences fail to fully explain disparities. Black women in the United States in particular experience disproportionately high levels of chronic stress, especially secondary to individual, institutional, overt or covert racism or other adverse life events, which may contribute to racial and ethnic disparities in infant mortality. On a macroenvironmental level, there is evidence of increased risk for infant mortality in areas with higher racial and economic segregation. It is often difficult to separate race and social class. Nonetheless, Black women who are exposed to interpersonal racism are at high risk for an adverse birth outcome. Black women who delivered a preterm infant are more likely to have experienced lifelong interpersonal racism than Black women who delivered term infants. In addition, chronic worry about racial discrimination also increases the risk of preterm birth.

There is also evidence that barriers preventing minority groups from accessing high-quality care contribute to and perpetuate perinatal health disparities. Despite a narrowing in the disparity gap for some neonatal care practices and certain outcomes, evidence in the last decade still shows substantial disparities in necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), **intraventricular hemorrhage (IVH),** infections, and other outcomes. In addition to complications during treatment in the NICU, there are also racial and ethnic differences in post discharge access to care and post neonatal morbidities. In one study, Hispanic and Black preterm infants were more likely to be readmitted and to die after discharge from the NICU than White infants, particularly infants with respiratory distress syndrome and BPD.

Congenital Malformations

Infant deaths from **congenital malformations** are the leading cause of infant deaths. Many disorders reside in this category, with **congenital heart disease** the leading etiology. Genetics may play a role in many congenital anomalies. The underlying molecular basis of many anomalies including

Table 114.2 Gestational Age and Birthweight Characteristics by Plurality: United States, 2020

PLURALITY	NUMBER OF BIRTHS	PERCENT			
		PERCENTAGE EARLY PRETERM*	PRETERM†	VERY LOW BIRTHWEIGHT‡	LOW BIRTHWEIGHT§
All births	3,613,647	2.7	10.09	1.34	8.24
Singleton	3,498,335	2.11	8.42	1.06	6.68
Twin	112,437	19.19	59.94	8.97	54.77
Triplet	2,738	65.78	98.72	35.79	95.17
Quadruplet	108	89.81	93.52	71.30	93.52
Quintuplet and higher-order multiples	29	100.00	100.00	86.21	100.00

*Early preterm is less than 34 completed weeks of gestation.
†Preterm is less than 37 completed weeks of gestation.
‡Very low birthweight is less than 1,500 g.
§Low birthweight is less than 2,500 g.
Source: National Center for Health Statistics, National Vital Statistics System, Natality.
From Osterman M, Hamilton B, Martin JA, Driscoll AK, Valenzuela CP. Births: Final data for 2020. *Natl Vital Stat Rep*. 2021;70(17):1–50.

Table 114.3 Factors That May Influence the Black-White Disparity in Preterm Birth

DOWNSTREAM FACTORS HYPOTHESIZED AS CAUSES OF THE BLACK-WHITE DISPARITY IN PRETERM BIRTH	WEIGHT OF THE EVIDENCE THAT THE FACTOR CONTRIBUTES TO THE BLACK-WHITE DISPARITY IN PRETERM BIRTH
Prenatal care	Plausible but existing literature generally does not support a role for quantitative measures of traditional prenatal care
Preconception care	Plausible contributing factor but little research available
Elective and indicated cesarean section	Plausible contributing factors but insufficient research
Substance use disorders	No published studies indicate that substance use explains the Black-White disparity in preterm birth (PTB)
Diet/nutrition	Plausible but more robust research needed
Gestational weight gain (GWG)	Unclear whether excessive or inadequate GWG contributes to the disparity
Obesity	Black women's higher obesity rates could contribute but cannot explain the disparity among nonobese women
Interpregnancy intervals	Potential small contributor
Age	Not a plausible cause of the disparity
Gestational diabetes (GDM)	May contribute but its greater effect size is balanced by lower prevalence among Black women
Hypertensive disorders of pregnancy (HDP)	Likely important contributor
Prepregnancy (preexisting) diabetes	Plausible but low prevalence among Black women
Prepregnancy (chronic) hypertension	Highly plausible but cannot explain PTB among women without this risk factor
Infection	Plausible but research inconclusive
Microbiota	Plausible
Neighborhood environmental exposures	Exposure to neighborhood social and physical hazards are highly plausible and potentially major contributors
Genetic and epigenetic factors	Genetic factors are unlikely to play a major role in the disparity (vs in PTB), epigenetic factors may be important
MIDSTREAM CAUSES (WHICH EXERT THEIR EFFECTS THROUGH DOWNSTREAM FACTORS)	
Stress	Likely a major contributor through neuroendocrine mechanisms. More research needed on life-course (vs pregnancy-only) stress
Social support	Plausible but research is inconsistent and has focused on support during pregnancy alone
Income and education	Plausible but relationships are complex due to racism
Childhood and lifelong socioeconomic status	Plausible but rarely measured
Wealth	Plausible but we did not identify literature on wealth and the PTB disparity
Educational quality	Plausible but we did not identify literature on educational quality and the PTB disparity
Neighborhood socioeconomic disadvantage	Highly plausible, considerable literature supports
UPSTREAM CAUSES	
Racism in multiple forms and through multiple pathways and biologic mechanisms	Highly plausible

A factor may influence PTB without influencing the racial disparity, unless it is more prevalent or has a stronger effect size among Black women (or women of European descent).
Modified from Braverman P, Dominguez TP, Burke W, et al. Explaining the Black-White disparity in preterm birth: a consensus statement from a multi-disciplinary scientific work group convened by the March of Dimes. *Front Reprod Health*. Sept 2021;3:Article 684207. Table 1.

well-described clinical syndromes, such as VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities), remain a mystery (see Chapter 100).

Specific interventions can reduce the potential for certain congenital malformations, most notably periconceptional folic acid intake, improved management of maternal diabetes, and appropriate vaccination programs to prevent diseases such as rubella during pregnancy. However, the mechanism of most congenital malformations remains poorly understood and therefore not yet amenable to population-based prevention strategies.

Sleep-Related Deaths (SUID, SIDS)

SUID is a sudden and unexpected death during infancy (see Chapter 423). Defined in 2006, this term is only used after a thorough investigation has been conducted including postmortem examination. Deaths due to SUID are categorized as (1) SIDS, (2) accidental suffocation or strangulation in bed (ASSB; or any other location), and (3) ill-defined or unknown causes. SUID infant deaths are primarily sleep related and are the most common reason for **post neonatal mortality**. SUID rates decline after 4 months of age. Risk factors for SUID include nonsupine sleep, maternal smoking during pregnancy, secondhand smoke exposure during infancy, bed-sharing, overheating/over bundling, soft bedding, loose blankets, bumper pads, and sleep locations other than an approved crib or bassinet. Protective factors include breastfeeding.

Preterm Birth

Preterm birth is defined as a live birth occurring before the 37th week of gestation. Worldwide, about 15 million infants (11% of live births) are born preterm, a rate ranging between 5% and 18% among all countries. In the United States, ~1 of 10 infants are born preterm, making the United States one of the 10 countries with the highest preterm birth rate (see Fig. 114.8). For the fifth year in a row, the U.S. preterm birth rate has steadily increased every year to 10.2% in 2019 from 9.6% in 2014. Racial and ethnic disparities in preterm birth also continue to exist (Table 114.3). Accurate calculation of gestational age is important to compare preterm births between countries or other jurisdictions; comparisons may be compromised due to the use of different methods to calculate gestational age. Three approaches are currently in use: **last menstrual period** (LMP), **obstetric estimate** (OE) by ultrasound examination in the first trimester, and a **combined estimate**. The last defers to the LMP *unless* the value is missing from the vital record information or is extremely inconsistent with the recorded birthweight. In this circumstance (0.4% of birth records in 2013) the combined method uses the OE value. The OE offers superior validity. Since 2014, reports by federal agencies and stakeholder organizations (e.g., March of Dimes) use the OE to state preterm birth rates. The OE is typically a 1–2% lower preterm birth rate than the LMP or combined method. In 2016, the national preterm birth rate based on OE was 9.84%, compared to an 11.40% rate using the combined method.

Mortality rate, incidence of complications, and risk for serious disability due to preterm birth increases as gestational age decreases (see Fig. 114.4). Subcategories of preterm birth based on gestational age have been defined given important differences in morbidity and mortality risk. These are late preterm (34-36 6/7 weeks), moderate preterm (32-33 6/7 weeks), very preterm (28-31 6/7 weeks), and extremely preterm (less than 28 weeks). From an infant mortality perspective, *extremely preterm* births have substantial importance, because >50% of all infant deaths occur in this population. Some risk factors associated with preterm delivery include multiple gestation pregnancy, short interpregnancy interval, maternal morbidity (e.g., smoking, substance abuse, chronic and metabolic diseases), maternal mental health (e.g., acute and chronic stress, depression), sociodemographic factors (e.g., SES, systemic and interpersonal racism and discrimination), and environmental factors (e.g., neighborhood pollution and crime). Potential candidate genes are suspected as being associated with preterm birth, and they are broadly grouped into six categories: innate immunity and inflammation, tissue modeling and biogenesis, endocrine system, vascular and angiogenesis, metabolism, and miscellaneous. Genome-wide association studies in Denmark, Norway, and Finland confirm robust associations between maternal loci and pregnancy duration (variants in *EBF1, EEFSEC, AGTR2, WNT4, ADCY5,* and *RAP2C*) and preterm birth (variants in *EBF1, EEFSEC,* and *AGTR2*). Genome and transcriptome profiling of spontaneous preterm birth phenotypes (e.g., spontaneous preterm birth, preterm premature rupture of membranes) also shows significant molecular signatures in preterm cases. These genetic results are preliminary but may not explain the majority of preterm births.

The Late Preterm Neonate

It is important to appreciate the significance of late preterm delivery (34-36 6/7 weeks). Among all preterm infants, ~75% are late preterm infants. Often these infants seem similar to their term counterparts, but they are at significantly higher risk for apneic episodes, disorders of thermoregulation (e.g., hypothermia), hypoglycemia, respiratory distress, feeding difficulties, dehydration, hyperbilirubinemia, and suspected sepsis. These issues are usually due to immaturity and limited compensatory responses to extrauterine life. Late preterm infants are more likely than term infants to require NICU admission and experience an extended hospital stay. They also appear to have poorer neurodevelopmental outcomes across a number of early and late developmental outcomes (such as attention-deficit disorders, social and behavioral problems, learning disabilities, and school failure) compared with full-term infant counterparts.

Late preterm deliveries may result from complications of pregnancy (e.g., chorioamnionitis, premature rupture of membranes) or maternal conditions (e.g., preeclampsia, placenta accreta, maternal vasa previa). Many are caused by elective delivery through induction of labor or scheduled cesarean birth during the late preterm period. Because of the elevated morbidity and mortality risk in late preterm infants, a recommendation to eliminate elective deliveries before 39 weeks' gestation gained international traction.

The Moderate and Extremely Preterm Neonate

As gestational age at delivery declines, morbidity and mortality risks increase (see Fig. 114.5). With modern neonatal intensive care, the potential for survival at a given gestational age has improved. With that, the *threshold* gestational age for offering comprehensive neonatal intensive care has correspondingly declined. However, assigning a specific gestational age for threshold of viability remains a challenging problem. Current published data suggest minimal life-sustaining impact for neonatal intensive care offered before 22-23 weeks' gestation. However, covariables such as birthweight and exposure to antenatal steroids must be considered. Neonates born at extremely early gestational ages are at very high risk for morbidities carrying lifelong consequences. When present, these life-threatening conditions can prolong the NICU length of stay or be the immediate cause of death. Therefore multidisciplinary decision-making with direct family participation is essential.

Preterm neonates at moderate and early gestational ages are at elevated risk for all the complications of prematurity. Additional categories of morbidity that are absent or extremely rare in the late preterm and term populations also become much more common at earlier gestational ages (Table 114.4). These include **adverse neurodevelopmental** sequelae such as cerebral palsy, periventricular leukomalacia, IVH, hydrocephalus, visual impairment, and hearing impairment. Problems affecting other major organ systems include BPD, NEC, and patent ductus arteriosus (PDA). Extremely preterm infants are at the highest risk for these complications, which also tend to be more severe when they occur in extremely preterm infants.

IVH etiology is multifactorial but attributed to the rupture of the very fragile capillaries of the periventricular white matter and choroid plexus. The typical pathophysiology is accumulation of blood in the lateral ventricles, which can lead to obstruction of cerebrospinal fluid circulation and ultimately hydrocephalus (posthemorrhagic hydrocephalus) and increased risk for white matter injury (periventricular leukomalacia).

BPD is a complication of respiratory distress syndrome and prematurity leading to reactive airway disease, alveolar insufficiency, and in severe cases, pulmonary hypertension, and death. BPD remains the

Table 114.4 Major Morbidities of the Neonate and Associated Etiologic Conditions

MORBIDITIES	EXAMPLES OF ETIOLOGY
CENTRAL NERVOUS SYSTEM	
Spastic diplegic/quadriplegic cerebral palsy	HIE, periventricular leukomalacia, undetermined factors
Choreoathetotic cerebral palsy	Kernicterus/bilirubin encephalopathy
Microcephaly	Intrauterine infections
Hydrocephalus	IVH, HIE, meningitis
Seizures	HIE, encephalopathies, hypoglycemia
Learning disorders, developmental delay	Prematurity, HIE, hypoglycemia, IVH
Visual impairment	ROP, strabismus, refractive errors, cerebral vision impairment
SENSATION: PERIPHERAL NEUROPATHIES	
Visual impairments	ROP, congenital viral infection
Strabismus	Opioid exposure, undetermined
Hearing impairment	HIE, bilirubin toxicity, drug toxicity (loop diuretics, aminoglycosides)
Speech delay	Prematurity, prolonged endotracheal intubation, hearing loss
Paralysis, paresis	Birth trauma (usually affected: phrenic nerve, brachial plexus, spinal cord)
RESPIRATORY SYSTEM	
Bronchopulmonary dysplasia	Prematurity, positive pressure ventilation, oxygen exposure
Subglottic stenosis	Prolonged endotracheal intubation
Sudden unexpected infant death	Prematurity, unsafe sleep conditions
Choanal stenosis, nasal septum injury	Prolonged nasotracheal intubation, nasal CPAP
CARDIOVASCULAR SYSTEM	
Cyanosis	Pulmonary hypertension, cor pulmonale, severe BPD
Heart failure	PDA, congenital heart defects with left-to-right shunting
GASTROINTESTINAL SYSTEM	
Short gut syndrome	NEC, malrotation with mid-gut volvulus, bowel atresia
Cholestatic liver disease	Injury from prolonged parenteral nutrition, sepsis, short gut syndrome
Failure to thrive	Short gut syndrome, BPD, cyanotic heart disease
Inguinal hernia	Preterm birth, male gender, positive pressure ventilation
MISCELLANEOUS	
Cutaneous scarring	Cutis aplasia, chest tube placement
Hypertension	Renal thrombosis, prolonged umbilical artery catheterization, unknown

BPD, Bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

most common morbidity of prematurity among NICU survivors. The most powerful predictor of BPD is gestational age; as gestational age decreases, the risk of BPD increases. Oxygen exposure and treatment with positive pressure ventilation also increase the risk of developing BPD at any gestational age.

NEC is an inflammatory process that can occur anywhere in the lower gastrointestinal tract, most often at the distal ileum and ascending colon. In approximately 40% of patients, surgical exploration and resection of necrotic bowel is required, increasing potential for failure to thrive, malabsorption, and short bowel syndrome. Those at the lowest gestational ages are at the highest risk. Interestingly, preterm infants at the earliest gestational ages tend to develop NEC later in their hospital course than moderate or late preterm infants, suggesting a developmental window of susceptibility.

PDA is a common finding in preterm neonates born before 28 weeks. The ductus arteriosus must be patent during intrauterine life to sustain fetal circulation. Under normal physiologic conditions, the ductus undergoes functional closure within a few minutes of parturition. However, under conditions of marginal oxygenation and ventilation, ductal closure in preterm infants may be delayed. If ductal patency persists, it can promote pulmonary overcirculation, complicating the management of respiratory disease.

Retinopathy of prematurity (ROP) is a disorder characterized by abnormal proliferative vascularization of the retina that can lead to retinal detachment and blindness. It primarily affects LBW infants (≤1,500 g) and infants born at 30 weeks' gestation or less.

Low Birthweight, Intrauterine Growth Restriction, and Small for Gestational Age

LBW is classified as any live birth <2,500 grams. The **very low birthweight (VLBW)** subcategory corresponds to <1,500 g. In general, LBW and VLBW infants are also preterm, although other intrauterine conditions discussed later also contribute. **Intrauterine growth restriction (IUGR)** refers to deficiency of fetal growth and an abnormal fetal growth trajectory. Etiologies of IUGR include fetal factors (e.g., congenital infections including rubella and cytomegalovirus), congenital conditions (e.g., aneuploidy, such as trisomy 13, 18, and 21; malformations; genetic syndromes), placental insufficiency, placental structure and cord anatomy, and maternal factors (i.e., chronic and metabolic disease, exposure to medications and substances [tobacco exposure]). In contrast, **small-for-gestational-age (SGA)** neonates are constitutionally normal, without known genetic abnormalities or pathologic conditions. SGA and IUGR may occur at any gestational age. Birthweight and gestational age combine to predict mortality and morbidity risk at any gestational age.

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114.1 Race, Class, and Birth Outcomes

Richard J. David, James W. Collins Jr., and Gabriel Culbert

Clinicians understand the basic biologic processes underlying health and disease, but application of the biomedical model focused on the individual can preclude other dimensions of understanding. An **ecosocial model** explicitly involves simultaneous attention to causal factors acting at different levels, from the cellular to the societal.

Since 2000, the U.S. infant mortality rate has shown stark **inequity** between social groups. For example, for Black infants there are 10.8 infant deaths per 1,000 live births in 2018 compared with 4.6 per 1,000 live births for Whites. Racial **disparities** within the United States have worsened over the decades with slower declines in Black infant mortality (2.6% annually) compared to White infants (3.1% annually), thereby widening the gap from 43% in 1920 to 122% in 2017. A less well-recognized fact is that birth outcomes also show a steep gradient by social class within racial and ethnic groups in the United States. Still, White women who have not completed high school have a lower infant mortality rate than Black women who have graduated from college. Therefore both race and class are important factors. Moreover, the risk factor under study in much of health research comparing racial or ethnic groups is the effect of differential treatment associated with group membership, in other words, **racism**, not race per se.

KRIEGER'S ECOSOCIAL MODEL

The ecosocial model (Fig. 114.9) helps understand the impact of diseases, especially diseases with obvious social gradients, to move beyond a simplistic biomedical conception, focused on the

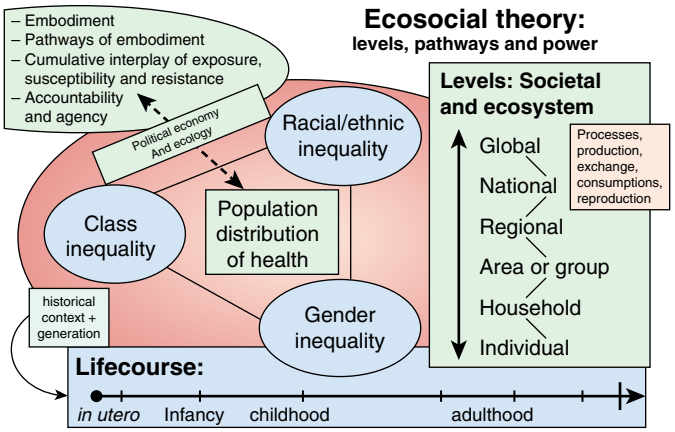

Fig. 114.9 Krieger's ecosocial model. (*From Krieger N. Epidemiology and the People's Health: Theory and Context. New York: Oxford University Press; 2011: Fig. 7-1; p. 214.*)

individual organism, to a more complete view that centers on social processes, including various dimensions of inequity. This model helps conceptualize health outcomes such as LBW and infant mortality by considering the real influences of social and environmental factors operating at various levels (individual, family, community) over time from fetal life through developmental stages to adulthood. At the core of the ecosocial model are societal level structures that strongly influence the pressures, constraints, supports, and access to positive resources that impact individuals, within the context of their communities and families, throughout the course of their lives. The net result at any point in time is a state of physical well-being or illness as the various beneficial and harmful influences are "embodied" through physiologic mechanisms. The value of an explicitly multilevel ecosocial model is in stimulating the formulation of hypotheses and designing studies that help us understand how important aspects of the social environment become embodied in adverse health outcomes by operating at various levels over the life course.

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Chapter 115

The Newborn Infant

Joanna J. Parga-Belinkie

See also Chapters 21 and 22.

The neonatal period is a highly vulnerable time as infants complete physiologic adjustments required for extrauterine existence. This transition is uneventful for most full-term infants. Management of the newborn should focus on parental anticipatory guidance, and early detection of conditions or complications that carry risk of morbidity or mortality.

115.1 Focused Peripartum History

Joanna J. Parga-Belinkie

Assessment of the newborn should begin with a review of the birth parent and family history, the pregnancy, and the delivery. When collecting a history special attention should be paid to the gender and sexual orientation of the family. Until prompted by the family, gender neutral terms such as birth parent, baby (no reference to gender), human milk, and nursing should be considered while collecting historical details. The healthcare professional should follow the family's lead on labeling in more gender and sexually specific terms. History should include the following information to guide evaluation and management in the newborn period.

BIRTH PARENT INFORMATION

- *Demographic and social data (socioeconomic status, age, race, perceived gender, sexual orientation, prenatal care utilization, substance use, education, zip code).* Newborns whose birth parents are young (<18 years old), or those who have housing concerns, food insecurity, or healthcare access issues may warrant evaluation by a social worker or case manager.
- *Medications taken in pregnancy.* Newborns exposed in utero to nonprescribed substances such as alcohol, cocaine, nicotine, and opioids should be evaluated for associated withdrawal symptoms (see Chapter 145). Other medications require review in partnership with a lactation consultant to ensure safe breastfeeding.
- *Medical conditions.* Including but not limited to: cardiopulmonary disorders, infectious diseases, genetic disorders, anemia, diabetes mellitus (see Chapter 147).
- *Family past medical history.* Including previous siblings with a history of jaundice (see Chapter 137).
- *Previous reproductive problems.* Stillbirth, prematurity, blood group sensitization (see Chapter 138).

CURRENT PREGNANCY AND DELIVERY

- Genetic screening (i.e., cell-free DNA, quad screen).
- Infectious assessments. Those requiring intervention in the newborn period include rapid plasma reagin (RPR) as a syphilis screen (see Chapter 264), HIV (see Chapter 322), herpes simplex virus (HSV), and hepatitis B (HepB; see Chapter 406).
  - Birth parents may be tested for SARS-CoV-2 (COVID-19). Current practice recommendations allow for rooming-in for the newborn and the birth parent if the parent is infected. Breastfeeding is not known to cause infection with SARS-CoV-2 and is recommended for the potential benefit of antibody transfer. Infection precautions such as masking, physical distancing, and handwashing should be followed (**COVID-19**, see Chapter 449.1).
- Imaging (fetal) results and consultation or follow-up for any fetal anomalies.
- History of preterm labor, placental issues, vaginal bleeding, acute illness (i.e., preeclampsia), duration of rupture of membranes.
- Description of the labor (duration, fetal presentation, fetal distress, fever) and delivery (cesarean section, anesthesia or sedation, use of forceps, Apgar scores, need for resuscitation).

This information, combined with clinical assessment of the newborn, will determine risk for clinical instability and need for monitoring and intervention.

115.2 Physical Examination of the Newborn Infant

Joanna J. Parga-Belinkie

Physical and behavioral characteristics of a healthy newborn infant are described in Chapter 22.

The **initial examination** of a newborn infant should be performed as soon as possible after delivery. Temperature, pulse, respiratory rate, oxygen saturation, color, tone, activity, and level of consciousness of infants should be monitored until stabilization. For high-risk deliveries, this examination should take place in the delivery room and focus on congenital anomalies, and pathophysiologic problems interfering with normal cardiopulmonary and metabolic extrauterine transition. Congenital anomalies may be present in 3–5% of infants. After a stable delivery room course, a second and more detailed examination should be performed within 24 hours.

If an infant remains in the hospital longer than 48 hours, repeat assessments should be performed daily throughout the hospital stay. For a healthy infant, the parents should be present during this examination. Explanation of the exam must be careful and skillful to address typical anatomic variations and address parental concerns. Infants should not be discharged from the hospital without a final examination because certain abnormalities (i.e., cyanosis and heart murmurs) may appear or disappear in the immediate neonatal period. The pulse (typical: 120-160 beats/min), respiratory rate (typical: 30-60 breaths/min), temperature, weight, length, head circumference, and any visible or palpable structural abnormality should be assessed. Blood pressure (BP) may be obtained if a neonate appears ill, or has a heart murmur. Pulse oximetry should be performed to screen for critical congenital heart disease (CHD) and is part of the routine screening for newborn infants.

Examining a newborn requires patience, gentleness, and procedural flexibility. Thus, if the infant is quiet and relaxed at the beginning of the examination, palpation of the abdomen or auscultation of the heart should be performed first, before other manipulations.

GENERAL APPEARANCE

Posture, activity, and tone can be accessed visually without touching the infant. Term infants may be well appearing lying in flexion with accompanying activity of the arms and legs, or in a more extended posture conserving energy for concerns like difficulty breathing. Coarse, tremulous movements with ankle or jaw **myoclonus** are more common and less significant in newborn infants than at any other age. Such movements tend to occur when an infant is active and are suppressible, whereas convulsive twitching usually occurs in a quiet state. Edema may produce a superficial appearance of good nutrition. Pitting after applied pressure may or may not be noted, but the skin over the extensor surfaces of the fingers and toes lacks the normal fine wrinkles when filled with edema fluid. Generalized edema may occur with prematurity, hypoproteinemia secondary to severe erythroblastosis fetalis, nonimmune hydrops, congenital nephrosis, Hurler syndrome, sepsis, and from unknown causes. Localized edema suggests a congenital malformation of the lymphatic system; when confined to one or more extremities of a female infant, it may be the initial sign of Turner syndrome (see Chapters 57 and 626).

SKIN

The skin in a newborn infant is dynamic and exam findings can change rapidly (see Chapter 688). Many of these findings are benign. Prompt identification and diagnosis can lead to rapid reassurance for families, or further workup for pathophysiology. Term and postmature infants tend to have thicker, paler, and better formed skin than premature infants. Premature infants tend to be ruddier in appearance, and depending on gestational age, the skin can be gelatinous. Many of the findings discussed in the following sections pertain to term and postdate infants.

Overall Appearance

The vernix, skin, and especially the umbilical cord may be stained brownish yellow if the amniotic fluid has been colored by the passage of meconium during or before birth. Transition to extrauterine life causes vasomotor instability with accompanying peripheral circulatory sluggishness. These are revealed by deep redness or purple lividity in a crying infant, or mottling and cyanosis. Mottling is another example of general circulatory instability, and is related to a transient fluctuation in skin temperature, particularly in lighter skinned infants. Mottling is seen in **cutis marmorata,** which is characterized by reticular mottling of the trunk and extremities and associated with hypothermia. At times it may be associated with more serious illness, such as in cutis marmorata telangiectasia congenita, where body asymmetry, cleft palate, and glaucoma can also be seen. Particular attention to temperature changes and evolution of mottling is essential. An extraordinary division of the body from the forehead to the pubis into red and pale halves (generally associated with dependent positioning) is known as harlequin color change, a transient and harmless condition.

Cyanosis refers to a bluish discoloration of either the skin or mucous membranes. Peripheral cyanosis is also referred to as **acrocyanosis** and refers to a bluish discoloration of the extremity or around the mouth (perioral cyanosis) associated with crying or cold. It generally resolves with rewarming. Central cyanosis can be seen when looking at the lips and mucous membranes. It may be masked by the pallor of vasoconstriction or anemia. Of note, the high hemoglobin content of the first few days and the thin skin may combine to produce an appearance of cyanosis at a higher partial pressure of arterial oxygen (Pao_2) than in older children. Localized cyanosis is differentiated from ecchymosis by the momentary blanching pallor (with cyanosis) that occurs after pressure.

Pallor may also be secondary to anemia, asphyxia, shock, or edema; careful attention should be paid to the birth history if pallor is suspected. The ruddy appearance of plethora is seen with polycythemia. Postterm infants may have a peeling, parchment-like skin (Fig. 115.1), a severe degree of which may mimic **ichthyosis congenita** (see Chapter 699). Scattered petechiae may be seen on the presenting part (usually the scalp or face) after a difficult delivery

Papules and Pustules

The most common pustular rash in White newborns (40–70%) is comprised of small, white papules on an erythematous base developing 1-3

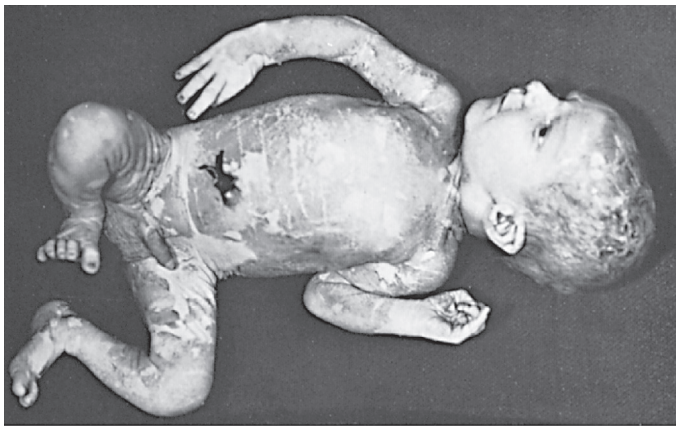

Fig. 115.1 Infant with intrauterine growth restriction as a result of placental insufficiency. Note the long, thin appearance with peeling, parchment-like dry skin, alert expression, meconium staining of the skin, and long nails. *(From Clifford S. Advances in Pediatrics. Vol 9. Chicago: Year Book; 1962.)*

days after birth. This benign rash, **erythema toxicum**, persists for as long as 1 week, contains eosinophils, and is usually distributed on the face, trunk, and extremities (see Chapter 688). **Milia,** another common skin finding, occurs in up to 50% of newborns. It is related to retention of keratin and sebaceous materials in glands and is commonly on the face but may also be present on the trunk, extremities, and on the penis in genetically male infants. **Epstein pearls** is a term for milia of the mouth. Milia is often confused with sebaceous hyperplasia, which also occurs in around 50% of neonates and is described as smooth yellow papules on the nose and upper lip. Both conditions resolve in a matter of weeks. **Pustular melanosis**, a benign lesion seen predominantly in Black neonates, contains neutrophils and is present at birth as a vesiculopustular eruption around the chin, neck, back, extremities, and palms or soles; it lasts 2-3 days. Both lesions need to be distinguished from more dangerous vesicular eruptions such as herpes simplex (see Chapter 299) and staphylococcal disease of the skin (see Chapter 227.1).

Birthmarks: Nonvascular

Slate-blue, well-demarcated areas of pigmentation called **congenital dermal melanosis (CDM)** are seen over the buttocks, back, and sometimes other parts of the body in more than 50% of Black, Native American, and Asian infants, and occasionally in White infants. They tend to disappear within the first year of life. Congenital nevi or congenital melanocytic nevi (CMN) occur in 0.2–2% of newborns. They can be black-brown, flat, or raised. Some have malignant potential and should be followed. Large nevi may need to be excised both for concerns for malignant potential and cosmetic reasons. Café-au-lait macules are flat, well circumscribed, and generally light brown in color occurring commonly on the torso, buttock, or lower extremity. Solitary lesions are common; multiple lesions can be associated with syndromes (i.e., McCune Albright, neurofibromatosis; see Chapters 689 and 636).

Birthmarks: Vascular

A key exam maneuver to detect a vascular lesion is blanching or placing pressure on the lesion to see if there is pale color change. The most common vascular stains present at birth are transient capillary vascular malformations, also referred to as nevus simplex or colloquially as salmon patches, stork bites, or angel's kisses. These transitory macular capillary hemangiomas are most commonly on the eyelids and neck and are described in Chapter 691. Cavernous or infantile hemangiomas are deeper, blue masses that have the potential to grow before involuting. Management is largely supportive unless the hemangiomas are large or located in a vital organ with the chance of cardiorespiratory instability as a result of their presence. Discussion of the management of hemangiomas is in Chapter 438.3.

SKULL AND SCALP

The skull may be molded particularly if the infant is the first-born, and the head has been engaged in the pelvic canal for a considerable time. **Caput succedaneum**, caused by scalp pressure from the uterus, cervix, or pelvis, appears as a circular boggy area of edema with indistinct borders and often with overlying ecchymosis. A **cephalohematoma** presents as a well-circumscribed fluid-filled mass that does not cross suture lines. Unlike caput succedaneum, cephalohematoma is often not present at delivery but develops over the first few hours of life. A **subgaleal hemorrhage**, which is not restricted by the boundaries of the sutures, is larger and more diffuse and may also appear behind the ears. Subgaleal hemorrhage (particularly associated with a bleeding disorder) requires prompt recognition because extensive bleeding may result in hypovolemic shock.

The head circumference of all newborns should be plotted on a growth chart to identify an excessively small head **(microcephaly)** or excessively large head **(macrocephaly)**. The diagnostic differential for microcephaly is broad and includes underlying genetic disorders, congenital infection, and intrauterine substance exposure (see Chapter 631). Macrocephaly can suggest hydrocephaly, storage disease, achondroplasia, neurocutaneous syndromes, or inborn errors of metabolism, or it may be familial.

The suture lines and the size and fullness of the anterior and posterior fontanels should be determined by palpation. The parietal bones tend to override the occipital and frontal bones. Premature fusion of sutures **(cranial synostosis)** is identified as a hard, immovable ridge over the suture and an abnormally shaped skull. This should be distinguished from plagiocephaly. **Deformational plagiocephaly** may be the result of in utero positioning forces on the skull and manifests as an asymmetric skull and face with ear malalignment (see Chapter 632). It is associated with torticollis and vertex positioning.

Great variation in the size of the **fontanels** exists at birth; if small, the anterior fontanel usually tends to enlarge during the first few months after birth. The persistence of excessively large anterior (normal: 20 ± 10 mm) and posterior fontanels has been associated with several disorders (Table 115.1). Persistently small fontanels may suggest microcephaly, craniosynostosis, and congenital hyperthyroidism, to name a few conditions. The presence of a third fontanel can be a normal variant, or present in conditions like trisomy 21. Soft areas **(craniotabes)** are occasionally found in the parietal bones at the vertex near the sagittal suture; they are more common in preterm infants and in infants who have been exposed to uterine compression. Such soft areas are usually insignificant; their possible pathologic cause should be investigated if they persist. Soft areas in the occipital region suggest the irregular calcification and wormian bone formation associated with osteogenesis imperfecta, cleidocranial dysostosis, lacunar skull, thyroid disorders, and occasionally Down syndrome.

Atrophic or alopecic scalp areas may represent **aplasia cutis congenita**, which may be sporadic, or autosomal dominant, or associated with: trisomy 13, chromosome 4 deletion, or Johanson-Blizzard syndrome. Depression of the skull (indentation, fracture, Ping-Pong ball deformity) is usually of prenatal onset and a result of prolonged focal pressure by the maternal pelvic bone.

FACE

The general appearance of the face should be noted with regard to **dysmorphic features,** which could be the result of genetic syndromes or deformational changes in utero. Genetic or congenital syndromes manifest in findings such as epicanthal folds, widely or narrowly spaced eyes, microphthalmos, asymmetry, long philtrum, and low-set ears. The face may be asymmetric as a result of a 7th cranial nerve palsy, hypoplasia of the depressor (depressor anguli oris) muscle at the angle of the mouth, or an abnormal fetal posture (see Chapter 100). Symmetric facial palsy suggests absence or hypoplasia of the 7th nerve nucleus **(Möbius syndrome)**.

Eyes

Lights should be dimmed for an eye examination. The eyes often open spontaneously if the infant is held up and tipped gently forward and backward. This maneuver, a result of labyrinthine and neck reflexes, is more successful for inspecting the eyes than forceful lid separation. Conjunctival and retinal hemorrhages are usually benign. Retinal hemorrhages are more common with vaginal delivery, especially those where vacuum or forceps were used. They resolve in most infants by 2 weeks of age (85%) and in all infants by 4 weeks. Pupillary reflexes are present after 28-30 weeks of gestation. The iris

Table 115.1 Disorders Associated with a Large Anterior Fontanel

Achondroplasia	Intrauterine growth restriction
Apert syndrome	Kenny syndrome
Cleidocranial dysostosis	Osteogenesis imperfecta
Congenital rubella syndrome	Prematurity
Hallermann-Streiff syndrome	Pyknodysostosis
Hydrocephaly	Russell-Silver syndrome
Hypophosphatasia	Trisomies 13, 18, and 21
Hypothyroidism	Vitamin D deficiency rickets

should be inspected for colobomas and heterochromia. A cornea >1 cm in diameter in a term infant with photophobia, tearing, or corneal clouding suggests congenital glaucoma and requires prompt ophthalmologic consultation. The presence of bilateral red reflexes suggests the absence of cataracts and intraocular pathology (see Chapter 659). **Leukokoria** (white pupillary reflex) suggests cataracts, tumor, chorioretinitis, retinopathy of prematurity, or a persistent hyperplastic primary vitreous and again warrants immediate ophthalmologic consultation (see Chapter 662).

Ears

Variation of the pinnae are often seen. Ear molding is a nonsurgical strategy to change the appearance of the external ear. Unilateral or bilateral preauricular skin tags occur frequently; if pedunculated they may warrant excision. Ears pits are also a common exam finding and may be associated with renal anomalies, so a thorough family history is warranted. The tympanic membrane, seen otoscopically through the short and straight external auditory canal, normally appears dull gray.

Nose

The nares should be symmetric and patent. The nose may be obstructed by mucus accumulated in the narrow nostrils. Infrequent suctioning with nasal saline lavage is recommended in this circumstance. Dislocation of the nasal cartilage from the vomerine groove results in asymmetric nares. Anatomic obstruction of the nasal passages secondary to unilateral or bilateral choanal atresia results in varying degrees of respiratory distress. Attempted passage of a nasogastric tube can help aid in this diagnosis.

Mouth

Examination should start with the lips to look for vermilion borders and the presence of a cleft. The soft and hard palate should be inspected and palpated for a complete or submucosal cleft, and the contour noted if the arch is excessively high or the uvula is bifid. A normal mouth may rarely have precocious dentition, with natal (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed. These teeth are shed before the deciduous tooth eruption (see Chapter 353). Removal of these teeth should be considered if there is concern for aspiration or if breastfeeding is affected. Neonatal teeth may occur in Ellis-van Creveld, Hallermann-Streiff, and other syndromes. Premature eruption of deciduous teeth is unusual and requires consultation with a pediatric dentist.

Neonates do not have active salivation. The tongue appears relatively large; the frenulum may be short indicating a tongue-tie or **ankyloglossia**. Debate exists around the use of a frenulectomy when ankyloglossia is seen on exam. Frenulectomy may reduce subjective birth parent nipple pain and improve latch technique and therefore overall breastfeeding duration. The cheeks have fullness on both the buccal and the external aspects as a result of the accumulation of fat in the sucking pads.

The throat of a newborn infant is difficult to visualize because of the low arch of the palate. Attempts should be made to clearly view the throat because posterior palatal or uvular clefts are easy to miss. The tonsils are small.

NECK

The neck appears relatively short. Abnormalities, while rare, include goiter, cystic hygroma, cystic structures (branchial cleft cysts, thyroglossal duct cysts), teratoma, hemangioma, and lesions of the sternocleidomastoid muscle. Muscular deformities can be traumatic or caused by a fixed positioning in utero that produces either a hematoma or fibrosis, respectively. Congenital **torticollis** causes the head to turn toward and the face to turn away from the affected side (see Chapter 721.1). Deformational plagiocephaly, facial asymmetry, and hemihypoplasia may develop if it is untreated (see Chapter 632). Redundant skin or webbing in a female infant suggests intrauterine lymphedema and Turner syndrome (see Chapters 57 and 626). The clavicles should be palpated for fractures.

CHEST

Breast tissue hypertrophy is common, and milk may be present in rare cases related to the birth parents' hormones. Asymmetry, erythema, induration, and tenderness suggest mastitis or a breast abscess. Supernumerary nipples, inverted nipples, or widely spaced nipples with a shield-shaped chest may be seen and warrant further genetic testing (i.e., Turner syndrome for shield-shaped chest).

LUNGS

Breathing should be observed. Normal variations in rate and rhythm are characteristic and fluctuate according to the infant's physical activity, state of wakefulness, or the presence of crying. Because fluctuations are rapid, the respiratory rate should be counted for a full minute with the infant in the resting state, preferably asleep. Under these circumstances, the usual rate for normal term infants is 30-60 breaths/min; in premature infants the rate is higher and fluctuates more widely. A rate consistently >60 breaths/min during periods of regular breathing that persists for >1 hour after birth is an indication to rule out pulmonary, cardiac, or metabolic etiologies. Preterm infants and some term infants may have **periodic breathing** characterized by periods of fast respirations, followed by a slowed respiratory rate, and in the case of prematurity potential apnea. Apnea is pathologic for a term infant and warrants further evaluation. Irregular gasping, sometimes accompanied by spasmodic movements of the mouth and chin, indicates impairment of the respiratory centers.

The breathing of newborn infants at rest is almost entirely diaphragmatic. During inspiration, the soft front of the thorax is usually drawn inward while the abdomen protrudes. If the baby is quiet, relaxed, and with good color, this paradoxical movement or "belly breathing" does not necessarily signify insufficient ventilation. On the other hand, labored respiration with intercostal retractions or tracheal tugging is evidence of respiratory distress and warrants further evaluation. Other signs of distress include nasal flaring, diminished breath sounds, rhonchi, and central cyanosis. A weak, persistent or intermittent groaning, whining cry, or **grunting** during expiration can at delivery signify issues with transitioning and oxygenation. If persistent it may be a sign of cardiopulmonary disease or sepsis and warrants immediate attention. When benign, the grunting resolves 30-60 minutes after birth. Stridor is a high-pitched sound associated with airway obstruction and may be present on inspiration and expiration or be biphasic. The type of stridor is dependent on the location of possible obstruction.

HEART

Auscultation is the primary examination technique for cardiac evaluation. Heart sounds should be heard on the left side of the chest; if sounds are more prominent on the right dextrocardia may be present. Typical pulse is 110-140 beats/min at rest but may vary normally from 90 beats/min in relaxed sleep, to 180 beats/min during activity. If the rate exceeds 200 beats/min and the infant is in a resting state, concern for supraventricular tachycardia warrants an electrocardiogram (ECG). Preterm infants usually have a higher resting heart rate, up to about 160 beats/min. In addition to auscultation, infant's pulses should be palpated in the upper and lower extremities to rule out **coarctation of the aorta** on admission and prior to discharge.

Transitory murmurs usually represent a closing ductus arteriosus or patent foramen ovale (PFO). Although CHD may not initially produce a murmur, a substantial portion of infants in whom persistent murmurs are detected during routine neonatal examination have underlying congenital heart malformation. Routine screening for critical CHD using pulse oximetry is performed between 24 and 48 hours of life, which overall yields a sensitivity approaching 80% and specificity >99%. Pulse oximetry screening with So_2 of ≥95% in the right hand or either foot and <3% difference between the right hand and foot is considered a normal screening test. Those with So_2 <95% should be referred for evaluation and possible echocardiogram (see Chapter 474). BP measurements are indicated in the evaluation of ill-appearing infants and those in whom CHD is suspected. Mean BP values vary by

gestational age; however, for all neonates BP is expected to rise in the first 72 hours after birth (Fig. 115.2).

ABDOMEN

The liver is usually palpable, sometimes as much as 2 cm below the rib margin. Less often, the tip of the spleen may be felt. The approximate size and location of each kidney can usually be determined on deep palpation and encircling of the flank. At no other period of life does the amount of air in the gastrointestinal tract vary so much. The intestinal tract is gasless at birth. Gas is swallowed soon after birth, and gas should be present in the rectum on radiograph by 24 hours of age. The abdominal wall is typically weak, and diastasis recti and umbilical hernias are common.

Unusual masses should be investigated immediately with ultrasonography. Renal pathology is the cause of most neonatal abdominal masses. Cystic abdominal masses include hydronephrosis; multicystic-dysplastic kidneys; adrenal hemorrhage, hydrometrocolpos; intestinal duplication; and choledochal, ovarian, omental, or pancreatic cysts. Solid masses include neuroblastoma, congenital mesoblastic nephroma, hepatoblastoma, and teratoma. A solid flank mass may be caused by renal vein thrombosis, which becomes clinically apparent with hematuria, hypertension, and thrombocytopenia. Renal vein thrombosis in infants is associated with polycythemia, dehydration, maternal diabetes, asphyxia, sepsis, nephrosis, and hypercoagulable states such as antithrombin III and protein C deficiency.

Abdominal distention at birth or shortly afterward may suggest an atresia or obstructive process or perforation of the gastrointestinal tract. This can be the result of meconium ileus, sepsis, or peritonitis. The failure to pass stool could represent a more distal obstruction (i.e., Hirschsprung disease, imperforate anus, or anal atresia) and a complete anal exam would be warranted (see later). A scaphoid abdomen in a newborn suggests a diaphragmatic hernia. Abdominal wall defects produce an omphalocele when they occur through the umbilicus and gastroschisis when they occur lateral to the midline (see Chapter 144). Omphaloceles are associated with other anomalies and syndromes, such as Beckwith-Wiedemann, trisomy 18, meningomyelocele, and imperforate anus. **Omphalitis** is an acute local inflammation of the periumbilical tissue that may extend to the abdominal wall, the peritoneum, the umbilical vein or portal vessels, or the liver and may require hospitalization with antibiotic treatment. The umbilical cord should have two arteries and one vein. A single umbilical artery is associated with an increased risk for a congenital or an occult renal anomaly.

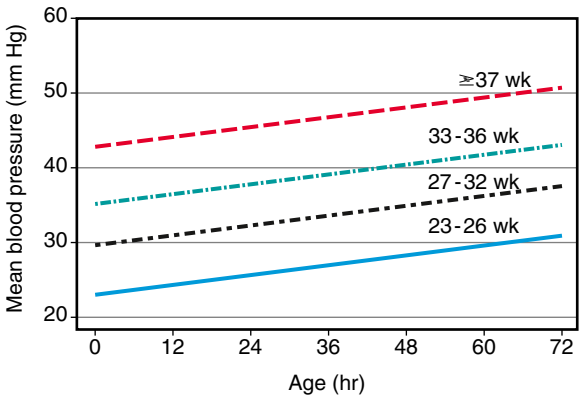

Fig. 115.2 Nomogram for mean blood pressure (BP) in neonates with gestational ages of 23-43 wk. Derived from continuous arterial BP measurements obtained from 103 infants admitted to the neonatal intensive care unit. The graph shows the predicted mean BP of neonates of different gestational ages during the first 72 hours of life. Each line represents the lower limit of the 80% confidence interval (two-tail) of the mean BP for each gestational age-group; 90% of infants for each gestational age-group will be expected to have a mean BP value equal to or greater than the value indicated by the corresponding line, the lower limit of the confidence interval. *(From Nuntnarumit P, Yang W, Bada-Ellzey SB. Blood pressure measurements in the newborn. Clin Perinatol. 1999;26:976–996.)*

GENITALS

The genitals and mammary glands typically respond to transplacentally acquired hormones. This can produce enlargement of the breasts in both sexes, and prominence of the genitals in females, often with leukorrhea. These transitory manifestations require no intervention. An imperforate hymen or other causes of vaginal obstruction may result in hydrometrocolpos and a lower abdominal mass (Fig. 115.3).

A normal scrotum at term is relatively large; its size may be increased by the trauma of breech delivery or by a transitory **hydrocele**, which is distinguished from a hernia by palpation and transillumination. The testes should be in the scrotum or should be palpable in the canals in term infants. Bilateral undescended testicles warrant an ultrasound evaluation, and a unilateral undescended testicle should be followed for several months to watch for descent before referral to pediatric urology is made. The scrotum may be ecchymotic from breech presentation or a retroperitoneal hemorrhage. Unilateral ecchymosis or erythema might prompt evaluation for testicular torsion, but this is rare in the newborn period. The prepuce or foreskin of a newborn infant is normally tight and adherent

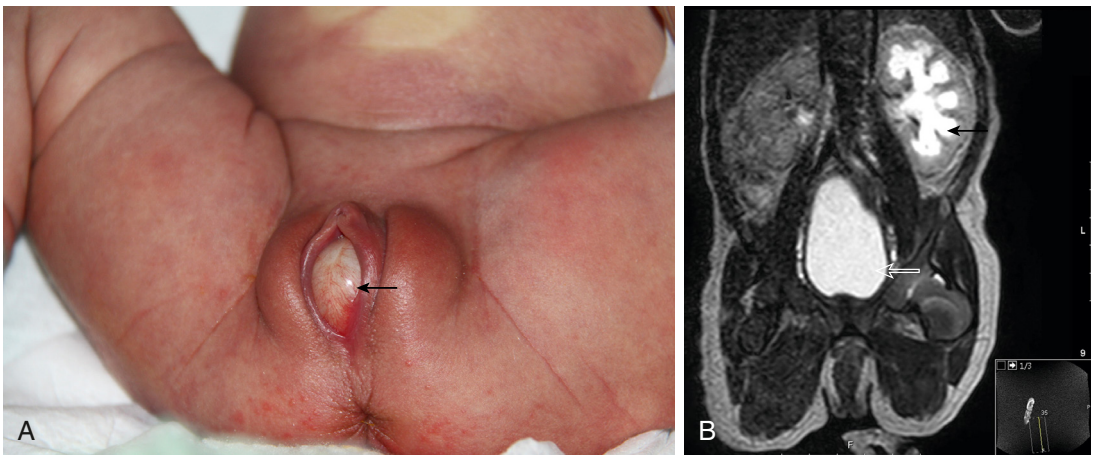

Fig. 115.3 Imperforate hymen. A, Examination revealed a bulge of the introitus characteristic of imperforate hymen. B, MRI demonstrated hydrometrocolpos *(open arrow)* with a 7.5-cm uterus. The enlarged uterus caused pressure on the left ureter, resulting in left hydronephrosis *(solid arrow). (From Peleg D, Shinwell ES. Newborn imperforate hymen resulting in hydronephrosis. J Pediatr. 2019;207:258. Fig. A & B.)*

to the penile glans at birth and cannot be retracted. The foreskin should separate naturally over several months. Severe hypospadias or epispadias should always suggest either that abnormal sex chromosomes are present (see Chapter 99) or that the infant is a masculinized female with an enlarged clitoris, because this finding may be the first evidence of adrenogenital syndrome (see Chapter 616). Erection of the penis is common and anticipatory guidance on this can be given. Urine is usually passed during or immediately after birth; a period without voiding may normally follow. Most neonates void by 12 hours of life.

ANUS

Some passage of **meconium**—the first tarry black stools of an infant—usually occurs within the first 12 hours after birth; 99% of term infants and 95% of premature infants pass meconium within 48 hours of birth. Physical examination is usually sufficient for diagnosis of imperforate anus, if the anal opening is absent or incorrectly located. However, if there is a fistula to the skin, urethra, or vagina, a newborn can pass meconium; in such cases, unless a careful exam is done, imperforate anus may not be discovered. All newborns with anorectal malformations warrant evaluation for possible associated cardiac, renal and spine anomalies (VACTERL association; see Chapter 100.1).

When examining the rectum, the lower spine should also be examined. A dimple or irregularity in skinfold present in the sacrococcygeal midline can be a typical exam finding, or it may represent a potential neurocutaneous sinus warranting ultrasound evaluation.

EXTREMITIES

During examination of the extremities, infants tend to rest in flexion. The effects of fetal posture (see Chapter 713) should be noted. Such examinations are particularly important after breech presentations when the hips can be significantly abducted. The hips of all infants should be examined with specific maneuvers to rule out congenital dislocation (see Chapter 719.1). A fracture or nerve injury associated with delivery can be detected by observation of the extremities in spontaneous or stimulated activity. The hands and feet should be examined for polydactyly, syndactyly, and abnormal dermatoglyphic patterns such as a single palmar crease.

NEUROLOGIC EXAMINATION

In utero neuromuscular diseases associated with limited fetal motion (fetal akinesia deformation sequence) produce a constellation of signs and symptoms independent of the specific disease. Severe positional deformations and contractures produce **arthrogryposis**. Other manifestations of fetal neuromuscular disease include breech presentation, polyhydramnios, primary apnea, pulmonary hypoplasia, dislocated hips, undescended testes, thin ribs, and clubfoot. Many congenital disorders manifest as hypotonia, hypertonia, or seizures, so a thorough history and broad differential must be explored.

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115.3 Routine Newborn Care

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The initial steps of management for all newborns after delivery are to warm, dry, and stimulate. One should simultaneously evaluate respiratory effort, heart rate, and color to determine next steps if resuscitation is needed. Full-term, vigorous infants may initially be placed on the mother's abdomen or chest after delivery, during which time **delayed cord clamping** (30-60 seconds) is recommended to improve transitional circulation and increase neonatal red blood cell (RBC) volume. 'In preterm infants delayed cord clamping of at least 120 seconds may improve survival. Umbilical cord milking particularly in preterm neonates is not recommended. Clearing the mouth of secretions with gentle suction with a bulb syringe or soft catheter is indicated if there is copious fluid in the mouth or nares. Spontaneously breathing neonates without distress require no assisted method to clear their airway.

The **Apgar score** is a practical method of evaluating infants immediately after birth and is assessed at 1 and 5 minutes of life (Table 115.2). Most healthy infants who are well appearing may remain in skin-to-skin contact with their mothers for bonding and nursing. Infants who fail to transition may lack a sustained respiratory effort, have a heart rate <100 beats/min, or persistent central cyanosis and should be placed under warmers for resuscitation and monitoring (see Chapter 123). Apgar scores should be one of many factors used to determine need for resuscitation. Changes in Apgar scores at sequential time points after birth reflect how well the infant is responding to resuscitation. If the 5 minute score remains <7, additional scores should be assigned every 5 minutes for up to 20 minutes. In addition to fetal distress, a number of factors including prematurity, delivery under general anesthesia, placental emergencies such as abruption, or uterine rupture, and concerns for hypoxic ischemic encephalopathy can result in low Apgar scores (Table 115.3).

MAINTENANCE OF BODY HEAT

Newborn infants are at risk for heat loss and hypothermia for several reasons. Relative to body weight, the body surface area (BSA) of a newborn infant is approximately 3 times that of an adult. Generation of body heat depends in large part on body weight, but heat loss depends on BSA. In low birthweight and preterm infants, the insulating layer of subcutaneous fat is thin. The estimated rate of heat loss in a newborn is approximately 4 times that of an adult. Under the usual delivery room conditions (20–25°C [68–77°F]), an infant's skin temperature falls approximately 0.3°C (0.54°F)/min, and deep body temperature decreases approximately 0.1°C (0.18°F)/min during the period immediately after delivery; these rates generally result in a cumulative loss of 2–3°C (3.6–5.4°F) in deep body temperature (corresponding to a heat loss of approximately 200 kcal/kg). The heat loss occurs by four mechanisms: convection of heat energy to the cooler surrounding air, conduction of heat to the colder materials touching the infant, heat radiation from the infant to other nearby cooler objects, and evaporation from skin and lungs.

Table 115.2 Apgar Evaluation of Newborn Infants*

SIGN	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

*At 60 seconds after complete birth of the infant (disregarding the cord and placenta), the five objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0-3 indicates an infant requiring immediate resuscitation.

Adapted from Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg.* 1953;32:260–267.

Table 115.3 Factors Affecting the Apgar Score*

Prematurity	Lung anomaly (diaphragmatic hernia)
Analgesics, narcotics, sedatives	Airway obstruction (choanal atresia)
Magnesium sulfate	Congenital pneumonia and sepsis
Acute cerebral trauma	Previous episodes of fetal asphyxia (recovered)
Precipitous delivery	Hemorrhage-hypovolemia
Congenital myopathy	Maternal acidosis
Congenital neuropathy	
Spinal cord trauma	
Central nervous system anomaly	

*Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

Metabolic acidosis, hypoxemia, hypoglycemia, and increased renal excretion of water and solutes may develop in term infants exposed to cold after birth because of their effort to compensate for heat loss. Heat production is augmented by increasing the metabolic rate and oxygen consumption in part by releasing norepinephrine, which results in nonshivering thermogenesis through oxidation of mainly brown fat. In addition, muscular activity increases. Hypoglycemic or hypoxic infants cannot effectively increase their oxygen consumption when exposed to a cold environment, and their central temperature decreases. After labor and vaginal delivery, many newborn infants have mild to moderate metabolic acidosis, for which they may compensate by hyperventilating. This response is more difficult for infants with central nervous system depression (asphyxia, medications) and infants exposed to cold stress in the delivery room. Therefore, to reduce heat loss, it is desirable to ensure infants are dried and either wrapped in blankets or placed with the birth parent or under radiant warmers. **Skin-to-skin contact** with the birth parent is the optimal method of maintaining temperature in the well-appearing newborn. Because carrying out resuscitative measures on a covered infant or one enclosed in an incubator is difficult, a radiant heat source should be used to warm the baby during resuscitation.

ANTISEPTIC SKIN AND CORD CARE

Nursery personnel should use alcohol-based solutions, or antiseptic soaps for routine handwashing before caring for each infant. Rigid enforcement of hand-to-elbow washing for 2 minutes in the initial wash, and 15-30 seconds in subsequent washes is essential for staff and visitors entering the nursery.

The World Health Organization (WHO) recommends an infant's first bath should be delayed until 24 hours of life to allow full transition to extrauterine life with emphasis on maternal–infant bonding, early breastfeeding, and achievement of temperature stability. Careful removal of the amniotic fluid and blood from the skin shortly after birth may reduce the risk of infection with blood-borne agents such as HIV and HepB; in these circumstances early bathing is warranted. Early bathing is also recommended for perinatal exposure to COVID-19. For the infant's first bath, the entire skin should be cleansed with warm water or a mild nonmedicated soap solution and rinsed with water to reduce the incidence of skin colonization with pathogenic bacteria and subsequent infectious complications. Cultural variation exists around umbilical cord care with a history of use of dyes, alcohols, and antiseptic solutions placed on the cord stump. Current American Academy of Pediatrics recommendations advise **dry cord care**. Dry cord care involves leaving the umbilical cord exposed to air or loosely covered, cleaning it with soap and water if it becomes soiled, and not submerging the infant in water to allow the stump to spontaneously fall off in 10-14 days. To avoid heat loss during a bath, the infant should then be dried and wrapped in clean blankets. Colonization and infection of newborns from potentially pathogenic organisms can also be reduced through continuous rooming-in with their birth parents, which creates an environment conducive for colonization from less pathogenic bacteria acquired from the birth parent's flora.

Vernix—a white cream like biofilm coating of the infant in utero—is spontaneously shed within 2-3 days, much of it adhering to the clothing, which should be changed daily. The diaper should be checked before and after feeding and when the baby cries; it should be changed when wet or soiled. The perineal area can be cleaned with unscented, preservative-free baby wipes or with mild soap and warm water.

NEWBORN PROPHYLAXIS AND SCREENING

Newborn assessment and vital sign monitoring may vary by hospital but generally decreases in frequency after the first 1-2 hours after birth. For well-appearing newborns, a reasonable interval between assessments is 4 hours during the first 2-3 days of life and 8-12 hours thereafter. The infant's temperature should be taken by axillary measurement, with a normal range of 36.5–37.4°C (97.7–99.3°F). Weighing at birth and daily thereafter is important because infants do lose weight, but should not lose more than 10% of their birth weight prior to hospital discharge. Excessive weight loss is grounds for a complete feeding evaluation, lactation support if chest feeding, and potential workup for issues related to failure to thrive if applicable.

The eyes of all infants, including those of cesarean birth, must be protected against gonococcal ophthalmia neonatorum by application of a 1-cm ribbon of erythromycin (0.5%) or tetracycline (1.0%) sterile ophthalmic ointments in each lower conjunctival sac. This procedure may be delayed during the initial short-alert period after birth to promote bonding, but once applied, drops should not be rinsed out (see Chapters 238 and 272.3).

Although hemorrhage in newborn infants can be a result of factors other than vitamin K deficiency, an intramuscular (IM) injection of 0.5-1 mg of water-soluble vitamin K_1 (phytonadione) should be given to all infants shortly after birth to prevent hemorrhagic disease of the newborn (see Chapter 142). Oral vitamin K is *not* considered effective as more research needs to be done on the amount of vitamin K, numbers of doses, time course of treatment, and gut metabolism in the infant for them to achieve the effectiveness of one IM dose.

HepB immunization before discharge from the nursery is recommended for newborns with weight >2 kg, irrespective of maternal hepatitis status. This dose should be given within 24 hours after delivery.

Neonatal screening is available for various genetic, metabolic, hematologic, and endocrine disorders. All states in the United States have adopted the recommendations of the Advisory Committee on Heritable Disorders in Newborns and Children, although the specific tests performed vary by state based in part on disease prevalence, detection rates, and costs (see Chapter 104). To be effective in the timely identification and prompt management of treatable diseases, screening programs must include not only high-quality laboratory tests but also follow-up of infants with abnormal test results; education, counseling, and psychologic support for families; and prompt referral of the identified neonate for accurate diagnosis and appropriate treatment.

Hearing impairment is a serious morbidity that affects speech and language development. Universal screening of infants is recommended to ensure early detection of hearing loss and appropriate, timely intervention. Testing for cytomegalovirus (CMV) should be considered with failed hearing screens as congenital CMV is the leading cause of nongenetic sensorineural healing loss (see Chapter 149.1). Parents of infants who fail screening should be counseled on the importance of screening results, reinforcing the need for prompt audiologic confirmation and emphasizing the potential for normal language development with prompt intervention.

Universal screening with pulse oximetry provides early detection of ductal dependent cyanotic CHD (see Chapter 474).

Universal screening for hyperbilirubinemia should include risk assessment in all infants with measurement of serum or transcutaneous bilirubin levels before hospital discharge (see Chapter 137.1).

Universal screening for congenital hip dysplasia with physical examination with the **Ortolani test** (sensation of the dislocated hip reducing) and **Barlow test** (unstable hip dislocating from the acetabulum) is recommended. Hip ultrasound is recommended for *positive exam findings*, or if the infant was breech in the third trimester, and it should be performed for most infants at 4-6 weeks after birth (see Chapter 719.1).

Screening for hypoglycemia in asymptomatic babies is risk based. It should be performed in infants who are small for gestational age, large for gestational age, born to birth parents who have diabetes (see Chapter 147) or were on medications known to lower infant blood glucose levels, were preterm, or had symptoms compatible with hypoglycemia. Acidosis and sepsis should also prompt evaluation for hypoglycemia.

For infants with suspected maternal chorioamnionitis or triple "I" (intrauterine inflammation, infection, or both), current clinical guidelines recommend laboratory screening for sepsis, including a blood culture, and 48 hours of broad-spectrum antibiotic therapy. However, evidence suggests a low incidence of sepsis among well-appearing, term neonates, and frequent, reliable observation to detect early signs of sepsis, with or without laboratory studies, may be appropriate (see Chapter 148).

Table 115.4 lists minimum criteria to be met before newborn discharge. A shortened hospital stay (<48 hours after delivery) is reasonable for healthy, term newborns but not always appropriate. Early discharge requires careful ambulatory follow-up at home (by a visiting nurse) or in the office within 24-48 hours of discharge.

Table 115.4 Criteria for Discharge of Healthy Term Newborns*

GENERAL
Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.5–37.4°C (97.7–99.3°F) in open crib
Physical examination reveals no abnormalities requiring continued hospitalization
Regular urination; stool × 1
At least two uneventful, successful feedings
No excessive bleeding 2 hr after circumcision
LABORATORY AND OTHER SCREENS
Maternal syphilis, hepatitis B surface antigen, COVID-19, and HIV status
Newborn hepatitis B vaccine administered
Maternal tetanus toxoid, reduced diphtheria toxoid, COVID-19, and acellular pertussis, adsorbed (Tdap) vaccination
Maternal influenza vaccination during flu season
Evaluation and monitoring for sepsis based on maternal risk factors including GBS colonization
Umbilical or newborn direct Coombs test and blood type if clinically indicated
Expanded newborn metabolic screening
Hearing screening
Screening for hypoglycemia based on infant risk factors
Pulse oximetry screening
Screening for hyperbilirubinemia, with management and follow-up as recommended based on level of jaundice
SOCIAL
Evidence of parental knowledge, ability, and confidence to care for the baby at home:
Feeding
Normal stool and urine output
Cord, skin, and genital care
Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)
Infant safety (car seat, supine sleep position, etc.)
Availability of family and physician support (physician follow-up)
Assessment of family, environmental, and social risk factors:
Substance misuse
History of child abuse
Domestic violence
Mental illness
Teen mother
Homelessness
Barriers to follow-up
Source of continuing medical care is identified

*Refers to infants born between 37 and 42 wk of gestation after uncomplicated pregnancy, labor, and delivery.
GBS, Group B streptococcus.
Data from American Academy of Pediatrics Committee on Fetus and Newborn. Hospital stay for healthy term newborn infants. *Pediatrics*. 2015;135:948–953.

Home Births

Planned home births are common in many countries and cultures. In the United States, they represent ~1% (~45,000) of all births; there has been a ~20% increase in home births perhaps related to the COVID-19 pandemic.

Many parents choose home birth as part of a lifestyle choice wanting a natural, family friendly birthing experience with a low risk of medical interventions. Home births have an approximately twofold increase in neonatal deaths (~1 per 1000).

Contraindications to home birth include preexisting maternal medical conditions, gestational age <37 weeks, multiple fetuses, nonvertex presentation, and prior cesarean section.

Most home births are performed by a certified midwife with expertise in neonatal resuscitation and accompanied by a second birthing attendant. After the birth of the child, the care of the newborn should be similar to institutional births.

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115.4 Male Circumcision

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Male circumcision consists of full or less often partial surgical removal of the foreskin from the penis. It is a very common procedure and performed across the globe. Circumcision performed during the newborn period has lower complication rates than when performed later in life. The procedure should only be performed in healthy stable newborns. Those providing circumcision should be adequately trained in sterile techniques and effective pain management to reduce risk of complications. The surgery includes dilation of the preputial orifice to visualize the glans, freeing the preputial epithelium from the epithelium of the glans, placement of the circumcision device (Gomco clamp, Plastibell, or Mogen clamp) to enhance hemostasis, and removal of foreskin. For pain management, topical 4% lidocaine (i.e., LMX4 cream), a dorsal penile nerve block, and a subcutaneous ring block are effective options. Topical anesthetic creams may cause a higher incidence of skin irritation in low birthweight infants; therefore penile nerve block techniques should be chosen for this group. Usually, the dorsal penile nerve block consists of injections of 0.4 mL of 1% lidocaine *without* epinephrine on both sides of the base of the penis. The subcutaneous circumferential ring block involves 0.8 mL of 1% lidocaine *without* epinephrine injected at the base or midshaft of the penis and may provide the most effective analgesia compared with other techniques. Nonpharmacologic techniques, such as positioning on a padded environment and use of sucrose pacifiers, are useful adjuncts to improve infant comfort during the procedure but are

insufficient as sole therapies to prevent procedural and postprocedural pain.

Contraindications to this procedure include critically ill infants, those with blood dyscrasias, individuals who have a family history of bleeding disorders (e.g., hemophilia), and those who have congenital abnormalities (e.g., hypospadias), congenital chordee, or deficient shaft skin (e.g., penoscrotal fusion, congenital buried penis). It should be confirmed before the procedure that the newborn received IM vitamin K in accordance with standard practice of newborn care. Premature infants may undergo circumcision before discharge.

Preventive health benefits of elective circumcision for male newborns include reductions in the risk of urinary tract infection in the first year of life, acquisition of sexually transmitted infections (HIV, human papillomavirus [HPV], HSV, and syphilis), and penile cancer. Acute complications from circumcision in the United States and other high-resource countries are rare but include bleeding, infection, and penile injury. More catastrophic injuries, including glans or penile amputation, are extremely rare. Later complications can include excessive residual skin (incomplete circumcision), excessive skin removal, adhesions, meatal stenosis, phimosis, and epithelial inclusion cysts.

Current evidence indicates that although health benefits outweigh the risks of male circumcision, health benefits are not substantial enough to recommend routine circumcision for all male newborns. Therefore physicians who counsel families about this decision should explain the potential benefits and risks in a nonbiased manner. The healthcare professional performing the procedure should ensure parents understand circumcision is elective. Ultimately, parents should decide whether circumcision is in the best interests of their child, weighing the medical information in context of their own religious, ethical, and cultural beliefs and practices.

Regardless of whether or not the newborn is circumcised, parents should be instructed in the care of the penis at discharge from the newborn hospital stay. The circumcised penis should be washed gently each day with soap and water. As part of normal healing, the glans may appear raw or yellowish for 7-10 days. Gauze with petroleum jelly can be used to cover the area and should be changed with each urine and stool until the glans heals.

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115.5 Parent–Infant Bonding

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See also Chapter 21.

Attachment of a newborn infant to their birth parent or a loving nonbiological caregiver is essential for their development. The attachment process may be important in enabling some birth parents and nonbiological caregivers to provide loving care during the neonatal period, and subsequently during childhood. The power of this attachment is so great that it enables the parents or nonbiological caregivers to make necessary schedule adjustments for the day-to-day care of the infant. Infants require 24-hour supervision including around the clock feedings, attending to crying, and so on. Parents or caregivers dedicate much of their lives to their children and this dedication extends past the newborn period.

Parent–infant bonding is initiated before birth with the planning and confirmation of the pregnancy. For the birth parent, there is a growing awareness of the baby as an individual, starting usually with the quickening or sensation of fetal movements. After delivery and during the ensuing weeks, sensory (visual, auditory, olfactory) and physical contact between the parents and baby triggers various mutually rewarding and pleasurable interactions. Touching an infant's cheek elicits the rooting reflex, which can help the infant locate a chest or bottle for feeding, and when breastfeeding nuzzling and licking of the nipple is a powerful stimulus for prolactin secretion in the birth parent. An infant's initial quiet alert state provides the opportunity for eye-to-eye contact, which is particularly important in stimulating the loving and possessive feelings of many parents for their babies. An infant's crying elicits the parental responses of touching the infant and speaking in a soft, soothing, higher-toned voice. These interactions are largely mediated by neuroendocrinologic mechanisms involving chemical signals from oxytocin and dopamine.

Initial contact between the birth parent and infant should take place in the delivery room, and opportunities for extended intimate contact and breastfeeding should be provided within the first hour after birth referred to as the "golden hour." Hospital routines should be designed to encourage parent–infant contact. Rooming-in arrangements, care by parents or dedicated caregivers, and family-centered care increase the opportunities for better parent–infant interaction.

Bonding is not an all or nothing activity nor is it time limited. Sick newborns in need of transport to another institution and their parents can develop effective bonding once they are reunited.

PARENTAL HUMAN MILK FEEDING AND ROOMING-IN (INCLUDES BREASTFEEDING AND CHESTFEEDING)

See Chapter 61 for full discussions of human milk and formula feeding.

Ample evidence indicates benefits to infants and birth parent when breastfeeding. One important hospital practice to encourage successful breastfeeding is rooming-in of newborns with their birth parent. Therefore it should be encouraged that term, healthy infants remain continuously in the birth parents' room when possible. To reduce the

Table 115.5 Ten Steps to Successful Parental Human Milk Feeding*

Every facility providing maternity services and care for newborn infants should accomplish the following:

1. Have a written feeding policy that is routinely communicated to staff and patients, comply with WHO restrictions on marketing of breast milk substitutes, and establish ongoing monitoring and data-management systems.
2. Ensure that staff have sufficient knowledge, competence, and skills to support breastfeeding.
3. Discuss the importance and management of breastfeeding with pregnant women and their families.
4. Facilitate immediate and uninterrupted skin-to-skin contact and help initiate breastfeeding as soon as possible after birth.
5. Support mothers to initiate and maintain breastfeeding and manage common difficulties.
6. Give newborn infants no food or drink other than breast milk unless medically indicated.
7. Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.
8. Support mothers to recognize and respond to their infants' feeding cues.
9. Counsel parents on the use and risks of feeding bottles, teats, and pacifiers.
10. Coordinate discharge to ensure timely access to ongoing support and care.

*Breastfeeding and chest feeding.
WHO, World Health Organization.
Adapted from WHO Guideline. Protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services. Geneva: World Health Organization; 2017.

Table 115.6 Drugs with Potential for Adverse Infant Effects During Parental Human Milk Feeding

CONTRAINDICATED	USE WITH CAUTION
Amphetamines	Alcohol
Antineoplastic agents	Amiodarone
Bromocriptine	Anthraquinones (laxatives)
Chloramphenicol	Aspirin (salicylates)
Clozapine	Atropine
Cocaine	β-Adrenergic blocking agents
Cyclophosphamide	Benzodiazepines
Doxorubicin	Birth control pills
Ecstasy (MDMA)	Bromides
Ergots	Cascara
Gold salts	Codeine
Heroin	Dicumarol
Immunosuppressants	Dihydrotachysterol
Methamphetamine	Domperidone
Phencyclidine (PCP)	Estrogens
Radiopharmaceuticals	Hydrocodone
Thiouracil	Lithium
	Marijuana
	Metoclopramide
	Meperidine
	Oxycodone
	Phenobarbital
	Primidone
	Reserpine
	Salicylazosulfapyridine (sulfasalazine)

risk of sudden infant death syndrome, safe sleep education should be given to families. Infants should be placed to sleep supine in a bassinet (preferably of clear plastic) to allow for easy visibility and care. There should be no extra bedding or toys present in the bassinet. The practice of swaddling an infant is controversial, but performed in many birth hospitals. Swaddling should never be performed once an infant has the ability to roll. All healthcare should be given to the infant in the bassinet, including the physical examination, clothing changes, temperature taking, skin cleansing, and other procedures. The clothing and bedding should be minimal, only enough needed for an infant's comfort, which is generally one more layer than the parent requires.

Additional practices that encourage successful breastfeeding include antepartum education and encouragement, immediate postpartum parent–infant contact with suckling, demand feeding, inclusion of all parents in breastfeeding education, and support from experienced healthcare professionals. Nursing at first for least 5 minutes at each breast is reasonable, allows a baby to obtain most of the available breast contents, and provides effective stimulation for increasing the milk supply. Nursing episodes should then be extended according to the comfort and desire of the chestfeeding parent and infant. The **Baby-Friendly Hospital Initiative**, a global effort sponsored by WHO and the United Nations Children's Fund to promote breastfeeding, recommends 10 steps to successful breastfeeding (Table 115.5). When instituted together as a complete bundle, these practices can improve multiple outcomes including breastfeeding initiation, duration of exclusive breastfeeding, and duration of overall breastfeeding. In the United States, however, many newborns are still not delivered in Baby-Friendly hospitals that have implemented all 10 steps. Educating mothers during pregnancy and showing mothers how to breastfeed are the most widely implemented strategies, whereas establishment of written breastfeeding policies, restriction of formula access, and establishment of breastfeeding support groups after discharge are among the most challenging to implement.

Medications and Breastfeeding

Only a small proportion of medications are contraindicated when breastfeeding. When weighing risks and benefits, healthcare providers should consider the following factors in discussion with the family: need for the medication, potential effects on lactation, extent of excretion into human milk, extent of oral absorption by the breastfeeding infant, potential adverse infant effects, proportion of feedings comprised of human milk, and age of the infant. For up-to-date information on drug levels in human milk and infant serum, possible adverse effects on infant health and lactation, and recommendations for possible medication alternatives, healthcare professional should refer to two different resources: LactMed (https://www.ncbi.nlm.nih.gov/books/NBK501922/) and the Infant Risk Center (https://www.infantrisk.com/).

Among U.S. women of childbearing age, nonprescribed substance use is on the rise. Opioid use disorder is of particular concern (see Chapter 145). For mothers desiring to breastfeed with a history of current or past substance use, healthcare professionals must carefully and thoughtfully weigh the documented benefits of human milk and breastfeeding against the risks associated with the substance that the infant may be exposed to during lactation. Most nonprescribed substances are found in human milk with varying degrees of oral bioavailability, and breast feeding is generally contraindicated (Table 115.6). However, mothers with substance use disorders should be encouraged to breastfeed under the following circumstances: established engagement in substance abuse treatment (e.g., methadone or buprenorphine maintenance therapy) including counseling and social support; abstinence from drug use for 30-90 days before delivery, with maternal urine toxicology testing at delivery negative other than prescribed substances; and engagement and compliance with outpatient care.

Contraindications to Breastfeeding

Medical contraindications to breastfeeding in the United States include infants with galactosemia, maple syrup urine disease, and phenylketonuria. Birth parent conditions that contraindicate breastfeeding include infection with human T-cell lymphotropic virus types 1 and 2, active tuberculosis (until appropriately treated ≥2 weeks and not considered contagious), herpesvirus infection on breast, Ebola virus infection, use of or dependence on nonprescribed substances, and birth parent treatment with some radioactive compounds (Table 115.7). Recommendations surrounding breastfeeding in HIV-infected mothers is changing. In resource-limited countries where diarrhea and pneumonia are significant causes of infant and child mortality, breastfeeding is recommended for HIV-positive mothers independent of receiving antiretroviral therapy. Studies from these resource-poor nations have shown undetectable viral loads do not equate to a zero risk of transmission via breastmilk to the infant. However, the chance of transmission is very low (<1%). Professional organizations in the United States are altering their approach from no breastfeeding, to partnering with families and counseling regarding risk mitigation strategies, particularly if use of human milk is important to families. Healthcare professionals can call the Perinatal HIV Hotline (888-448-8765) if they have questions on HIV and breastfeeding.

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Table 115.7 Summary of Infectious Agents Detected in Human Milk and Newborn Disease

INFECTIOUS AGENT	DETECTED IN HUMAN MILK?	HUMAN MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	PARENTAL INFECTION CONTRAINDICATION TO HUMAN MILK FEEDING?
BACTERIA			
Mastitis/*Staphylococcus aureus*	Yes	No	No, unless breast abscess present
Mycobacterium tuberculosis			
Active disease	Yes	No	Yes, because of aerosol spread, or tuberculosis mastitis
Purified protein derivative skin test result positive, chest radiograph findings negative	No	No	No
Escherichia coli, other gram-negative rods	Yes, stored	Yes, stored	—
Group B streptococci	Yes	Yes	No*
Listeria monocytogenes	Yes	Yes	No*
Coxiella burnetii	Yes	Yes	No*
Syphilis	No	No	No†
VIRUSES			
HIV	Yes	Yes	Depends on location and therapy. Ideally both parent and child on antiretroviral therapy In developed countries many recommend not to breastfeed, while in resource-limited countries, breastfeeding is encouraged
Cytomegalovirus			
Term infant	Yes	Yes	No
Preterm infant	Yes	Yes	Evaluate on an individual basis, but risk is increased
Hepatitis B virus	Yes, surface antigen	No	No, developed countries‡
Hepatitis C virus	Yes	No	No§
Hepatitis E virus	Yes	No	No
Human T-cell leukemia virus (HTLV)-1	Yes	Yes	Yes, developed countries
HTLV-2	Yes	Uncertain	Yes, developed countries
Herpes simplex virus	Yes	Yes	No, unless breast vesicles present
Rubella			
Wild type	Yes	Yes, rare	No
Vaccine	Yes	No	No
Varicella-zoster virus	Yes	No	No, cover active lesions**
Epstein-Barr virus	Yes	No	No
Human herpesvirus (HHV)-6	No	No	No
HHV-7	Yes	No	No
West Nile virus	Possible	Possible	Unknown
Zika virus	Yes	No	No
Ebola virus	Yes	Possible	Yes
COVID-19	Very rare and transient	No	No
PARASITES			
Toxoplasma gondii	Yes	Yes, one case	No

*Provided that the mother and child are taking appropriate antibiotics.
†Treat mother and child if active disease.
‡Immunize and immune globulin at birth.
§Provided that the mother is HIV seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.
**Provide appropriate antivaricella therapy or prophylaxis to newborn.
Adapted from Jones CA. Maternal transmission of infectious pathogens in breast milk. *J Paediatr Child Health*. 2001;37:576–582.

Chapter 116

High-Risk Pregnancies

Jourdan E. Triebwasser and Cara D. Dolin

The care of high-risk pregnancies should be coordinated with an experienced maternal-fetal medicine specialist.

High-risk pregnancies are those that increase the likelihood of maternal complications, miscarriage, congenital malformations, fetal growth restriction (FGR), preterm delivery, poor cardiopulmonary or metabolic transitioning at birth, fetal or perinatal morbidity and mortality, or intellectual impairment and other handicaps. A pregnancy may be high risk due to maternal disease, maternal age, fetal conditions, or pregnancy complications (Table 116.1). Social determinants of health, including housing, access to healthcare, food insecurity, health literacy, and effects of racism, also significantly impact the health of a pregnancy (see Chapter 114). There is no accepted comprehensive definition of what constitutes a *high-risk pregnancy*; therefore specific epidemiologic data regarding the incidence/prevalence cannot be reliably reported.

The lowest neonatal mortality rate occurs in infants of mothers who receive adequate prenatal care and who are 20-30 years of age. Pregnancies in both teenagers and people older than 40, particularly primiparous people, are at increased risk for FGR, fetal distress, preeclampsia, and stillbirth. Advanced maternal age increases the risk of both chromosomal and nonchromosomal fetal malformations (Fig. 116.1).

Maternal illness (Tables 116.2 and 116.3), infection (Table 116.4) and certain drugs (see Chapter 117.4) increase the risk for the fetus. The use of assisted reproductive technology (e.g., ovulation induction, in vitro fertilization, intracytoplasmic sperm injection) increases the risk of prematurity, perinatal mortality, infant morbidity, low and very low birthweight, imprinting disorders, and cerebral palsy. These risks are largely because of the increase in *multiple gestations* with such technology and the association with *prematurity*. The risks for *birth defects* are also increased with assisted reproductive technology, although the mechanisms are unclear.

Although assessing antepartum risk is important in reducing perinatal mortality and morbidity, some pregnancies become high risk only during labor and delivery; therefore careful monitoring is critical throughout the intrapartum course. Identifying high-risk pregnancies is important so that appropriate interventions and surveillance steps may be taken to reduce the risks to the fetus or neonate.

Table 116.1 Selected Factors Associated with High-Risk Pregnancy

PREEXISTING HEALTH CONDITIONS
Anemia (e.g., sickle cell anemia, iron deficiency)
Autoimmune disease (e.g., lupus, inflammatory bowel disease)
Chronic hypertension
Depression
Diabetes
Heart disease (congenital or acquired)
Kidney disease
Obesity
Organ transplant
Polycystic ovarian syndrome
Substance use disorder
Thyroid disease
Viral infection (e.g., HIV, hepatitis B, hepatitis C)
MATERNAL FACTORS
Access (delayed, absent) to prenatal care (uninsured)
Advanced maternal age (>35 years, higher risk if >40 years)
Alcohol, drug, medication, cigarette use
Infertility
Short interpregnancy interval (<18 mo between pregnancies)
Prior preterm birth, fetal anomaly, or fetal demise
Tobacco use
Young age
FETAL FACTORS
Aneuploidy
Congenital anomaly
Fetal growth restriction
Multiple pregnancy (twins, triplets, higher-order multiples)
OBSTETRIC COMPLICATIONS
Breech (abnormal) presentation
Gestational diabetes
Hypertensive disorders of pregnancy (including preeclampsia)
Oligohydramnios or polyhydramnios
Placenta accreta spectrum
Placenta previa
Placental abruption
Preterm premature rupture of membranes (PPROM)
Preterm labor

PRENATAL CARE

Early and regular prenatal care improve pregnancy outcomes for birthing people and their infants. Prenatal care should include (1) medical screening and treatment, (2) anticipatory guidance and education, and (3) psychosocial support. Because maternal and fetal health may change over the course of a pregnancy, care plans need to be reviewed and revised as appropriate. For high-risk pregnancies, interdisciplinary care plans may involve input from the family, support systems, obstetric care providers, neonatologist, geneticists, or other subspecialty providers. Prenatal care should begin in the first trimester with ongoing visits every 4 weeks until the third trimester, followed by visits every 2 weeks until 36 weeks, and weekly visits thereafter. Pregnancies complicated by maternal conditions (e.g., diabetes) or fetal conditions (e.g., monochorionic twins) require more frequent visits.

The American College of Obstetricians and Gynecologists (ACOG) recommends laboratory screening and immunization for all pregnant people (Table 116.5); additional screening may be indicated for populations at increased risk (e.g., third trimester sexually transmitted infection testing). *Patients should be offered screening and diagnostic testing for fetal chromosomal abnormalities in each pregnancy.*

Because many parents recognize only obvious clinical manifestations of genetic diseases, specific inquiry should be made about any disease affecting one or more blood relatives. A high index of suspicion should be maintained to the possibility of autosomal recessive disorders in

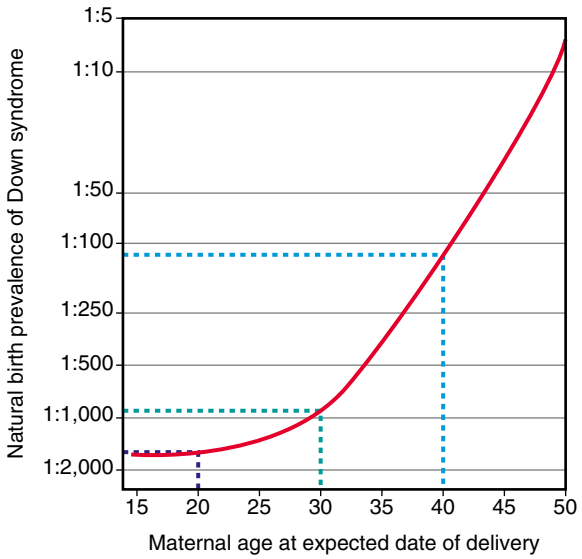

Fig. 116.1 Natural birth prevalence of Down syndrome according to maternal age. (*From Wald NJ, Leck I. Antenatal and Neonatal Screening. 2nd ed. Oxford: Oxford University Press; 2000.*)

Table 116.2 Maternal and Obstetric Conditions Affecting the Fetus or Neonate

CONDITION	RISK OF STILLBIRTH (PER 1,000 BIRTHS)	ADDITIONAL FETAL/NEONATAL CONSIDERATIONS
Antiphospholipid antibody syndrome	217-364	Low birthweight Preterm birth
Cholestasis	2-34	Preterm birth
Chronic hypertension	6-25	IUGR Preterm birth Antihypertensive exposure
Congenital heart disease	5-13	Congenital heart disease Preterm birth IUGR
Diabetes (gestational)	Uncertain if increased risk	LGA Brachial plexus injury Neonatal hypoglycemia Neonatal hyperbilirubinemia
Diabetes (pregestational)	9-20	LGA or IUGR (with maternal vascular disease) Congenital anomalies Brachial plexus injury Neonatal hypoglycemia Neonatal hyperbilirubinemia
Graves disease	3-7	Low birthweight Fetal thyrotoxicosis Neonatal Graves disease (1–5%) Congenital anomalies (related to thioamide exposure)
Hypertensive disorders of pregnancy Gestational hypertension Preeclampsia Eclampsia	9-51	Low birthweight Preterm birth
Hypothyroidism (poorly controlled)	Uncertain if increased risk	Low birthweight Impaired neuropsychologic development
HIV/AIDS	9-40	Preterm birth Congenital HIV Congenital anomalies (associated with some antiretroviral medications) Hematologic abnormalities (associated with some antiretroviral medications)
Idiopathic thrombocytopenic purpura	Possibly increased risk	Thrombocytopenia Intracranial hemorrhage Preterm birth
In vitro fertilization	12	Multiple pregnancy Congenital anomalies
Renal disease (chronic)	15-200	Preterm birth Low birthweight
Sickle cell anemia	81	Sickle cell anemia (if father is carrier or affected) Preterm birth Low birthweight
Substance use disorder	12.4 (alcohol >5 drinks/week) 12 (opioid use disorder)	Congenital anomalies (alcohol) Low birthweight Neonatal abstinence syndrome (opioids)
Systemic lupus erythematosus	40-150	Low birthweight Neonatal lupus, including rash Congenital heart block

LGA, Large for gestational age; IUGR, intrauterine growth restriction. Low birthweight = preterm, IUGR, or both.

offspring of couples who are closely related (i.e., consanguinity). Carrier screening should be available to all pregnant people. *ACOG currently recommends cystic fibrosis and spinal muscular atrophy screening for all with additional carrier screening recommended for certain populations.*

In addition to laboratory testing, ultrasound is recommended to establish pregnancy location, number, and gestational age (ideally in the first trimester) as well as identify structural malformations. Evaluation for structural malformations usually occurs in the second trimester, although advanced imaging may allow detection of several congenital anomalies in the first trimester. Additional ultrasound evaluation for fetal growth, assessment of amniotic fluid, or monitoring of structural malformations is often indicated in high-risk pregnancies.

Preterm birth is common in high-risk pregnancies (see Chapter 117), and screening for preterm birth is a part of prenatal care. Factors associated with prematurity (see Table 116.1) include multiple gestations and history of preterm birth, as well as biologic markers such as cervical shortening,

Table 116.3 Additional Maternal Conditions Affecting the Fetus or Neonate

DISORDER	EFFECT(S)	MECHANISM(S)
Assisted reproductive technology	Beckwith-Wiedemann, Silver-Russel, Angelman syndromes	Altered imprinting
Autoantibody against folate receptors	Neural tube defects	Blockage of cellular uptake of folate
Cervical neoplasia	Preterm premature rupture of membranes, preterm birth	Associated with loop electrosurgical excision procedure or cone therapy
Endemic goiter	Hypothyroidism	Iodine deficiency
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise	Autoantibody similar to that in bullous pemphigoid
Hyperparathyroidism	Neonatal hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Placental metastasis
Myasthenia gravis	Transient neonatal myasthenia	IgG antibody to acetylcholine receptor crosses placenta
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency	Genetic anticipation
NMDAR antibody encephalitis	Cortical dysplasia	Transplacental antibody
Obesity	LGA or IUGR, hypoglycemia	Unknown, similarities to diabetes
Phenylketonuria	Microcephaly, cognitive impairment	Elevated fetal phenylalanine values
Poor nutrition	IUGR, adult insulin resistance	Reduced fetal nutrients, nutritional programming
Renal transplantation	IUGR	Uteroplacental insufficiency
Rhesus or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	IgG crosses placenta and is directed to fetal cells with antigen

IgG, Immunoglobulin G; LGA, large for gestational age; NMDAR, antibody to *N*-methyl- D -aspartate receptor; IUGR, intrauterine growth restriction.

genital infection, presence of fetal fibronectin in cervicovaginal secretions, and abnormal serum α-fetoprotein (AFP). Second trimester cervical length screening by transvaginal ultrasound is currently the best clinical predictor of spontaneous preterm birth; however, universal transvaginal cervical length screening is not mandatory and transabdominal screening may be performed at the time of the anatomic survey. Short cervical length is frequently defined as less than 25 mm, with shorter lengths having increasing risk of preterm birth. Vaginal progesterone reduces the risk of preterm birth among people with a short cervix in the second trimester. For people with a history of spontaneous preterm birth before 34 weeks, serial transvaginal cervical length screening should be performed between 16 and 24 weeks with cerclage placement offered to those with a short cervix.

Many high-risk pregnancy conditions are associated with an increased risk of stillbirth compared with the population risk of approximately 6 per 1,000 births in the United States. Thus antenatal fetal surveillance is often a component of prenatal care. The common pathway for fetal demise in many high-risk pregnancies is fetal hypoxemia leading to acidosis. Fetal hypoxemia and acidosis alter fetal heart rate (FHR), movements, and renal function leading to oligohydramnios. Antenatal fetal surveillance in the form of nonstress test (NST), ultrasound fluid assessment, or biophysical profile (BPP) monitors for these changes to assess risk of stillbirth. Although there is limited evidence to support antenatal surveillance, it is a recommended part of antenatal care for multiple maternal, fetal, and placental conditions (see Table 116.2).

HIGH-RISK PREGNANCY IDENTIFIED BY ULTRASOUND

Ultrasound may be used to diagnose congenital anomalies before birth. However, the sensitivity of ultrasound depends on the lesion, fetal position or number, maternal body habitus, and experience of the performing clinician. For example, the detection rate of congenital heart disease in an unselected population is 45%. Although the detection rate of hypoplastic left heart is greater than 80%, conotruncal abnormalities are detected less than 50% of the time before the neonatal period.

Ultrasound should be performed when the uterus is inappropriately large or small for gestational age. A uterus large for the estimated stage of gestation suggests the presence of multiple fetuses, polyhydramnios, or a fetus with macrosomia. An inappropriately small uterus suggests oligohydramnios or poor fetal growth. The presence of **polyhydramnios**, **oligohydramnios,** or FGR indicates a high-risk pregnancy.

Amniotic fluid volume is variable throughout pregnancy and progressively increases from 10 to 30 weeks of gestation. On average, volume is typically <10 mL at 8 weeks and increases to 630 and 770 mL at 22 and 28 weeks, respectively. After 30 weeks, the rate of increase slows and the volume remains fairly constant until 36-38 weeks. This is followed by a progressive decline, with an average volume of 515 mL at 41 weeks of gestation.

Polyhydramnios complicates 1–3%, and oligohydramnios 1–5%, of pregnancies, although the true incidence of amniotic fluid disorders is confounded by the lack of a uniform approach to diagnosis. The ultrasound criteria for these diagnoses are based on either the *amniotic fluid index* (AFI) or a *deepest vertical pocket* (DVP). The AFI is determined by measuring the vertical dimension of amniotic fluid pockets in four maternal abdominal quadrants and reporting the sum of these values. Polyhydramnios is defined by an AFI ≥24 cm or a DVP ≥8 cm. Oligohydramnios is defined by an AFI <5 cm or a DVP <2 cm.

Polyhydramnios may lead to preterm labor or abruptio placentae, and it is associated with maternal diabetes, congenital anomalies, aneuploidy, and fetal neuromuscular dysfunction (Table 116.6). Increased fetal urination, as with congenital nephrotic syndrome, or edema formation, such as hydrops fetalis, is also associated with excessive amniotic fluid volume. Polyhydramnios may be categorized as mild (AFI 24-29.9 cm, DVP 8-11 cm), moderate (AFI 30.0-34.9 cm, DVP of 12-15 cm), or severe (AFI ≥35 cm, DVP ≥16 cm). Most cases of mild polyhydramnios are idiopathic. However, with increasing severity of polyhydramnios, the risk of a fetal abnormality increases significantly from 6–10% for mild to 20–40% for severe polyhydramnios. Additional abnormalities may be noted after birth, especially among those with severe polyhydramnios. Severe and symptomatic polyhydramnios may be managed by serial reduction

Table 116.4 Maternal Infections Affecting the Fetus or Newborn

INFECTION	MODE(S) OF TRANSMISSION	NEONATAL OUTCOME
BACTERIA		
Group B streptococcus	Ascending cervical	Sepsis, pneumonia
Escherichia coli	Ascending cervical	Sepsis, pneumonia
Listeria monocytogenes	Transplacental	Sepsis, pneumonia
Mycoplasma hominis	Ascending cervical	Pneumonia
Chlamydia trachomatis	Vaginal passage	Conjunctivitis, pneumonia
Syphilis	Transplacental, vaginal passage	Congenital syphilis
Neisseria gonorrhoeae	Vaginal passage	Ophthalmia (conjunctivitis), sepsis, meningitis
Mycobacterium tuberculosis	Transplacental	Prematurity, fetal demise, congenital tuberculosis
VIRUS		
Rubella	Transplacental	Congenital rubella
Cytomegalovirus	Transplacental, breast milk (rare)	Congenital cytomegalovirus or asymptomatic
HIV	Transplacental, vaginal passage, breast milk	Congenital or acquired immunodeficiency syndrome
Hepatitis B	Vaginal passage, transplacental, breast milk	Neonatal hepatitis, chronic hepatitis B surface antigen carrier state
Hepatitis C	Transplacental and vaginal passage	Rarely neonatal hepatitis, ~5% chronic carrier state possible
Herpes simplex type 2 or 1	Intrapartum exposure	Neonatal herpes simplex virus Neonatal encephalitis; disseminated viremia, or cutaneous infection
Varicella-zoster	Transplacental:	
	Early	Congenital anomalies
	Late	Neonatal varicella
Parvovirus	Transplacental	Fetal anemia, hydrops
Coxsackievirus B	Fecal-oral	Myocarditis, meningitis, hepatitis
Rubeola	Transplacental	Abortion, fetal measles
West Nile	Transplacental (rare) Possible perinatal	Uncertain, possible rash, encephalitis
Zika	Transplacental	Congenital microcephaly, intracranial calcifications, brain abnormalities, retinal lesions
Chikungunya	Transplacental (rare), perinatal	Neonatal encephalitis
Dengue	Transplacental, perinatal	Neonatal sepsis-like symptoms
PARASITES		
Toxoplasmosis	Transplacental	Congenital toxoplasmosis
Malaria	Transplacental	Abortion, prematurity, intrauterine growth restriction
FUNGI		
Candida	Ascending, cervical	Sepsis, pneumonia, rash

Table 116.5 Recommended Prenatal Fetal and Maternal Screening Tests and Preventative Care

FIRST TRIMESTER
Blood type and antibody screen
Complete blood count
Syphilis screen (VDRL/RPR or treponemal test)
Urinalysis or urine culture
Hepatitis B surface antigen
HIV
Chlamydia/gonorrhea*
Rubella immunity
Offered carrier screen for at risk populations
Offered ultrasonography (dates)
Offered cell-free DNA†
SECOND/THIRD TRIMESTER
Diabetes screen (24-28 weeks)
Complete blood count
Quad screen: α-fetoprotein, estriol, human gonadotropin, inhibin A
Rh antibody screen*
Group B streptococcus
Tdap and seasonal (influenza) vaccinations
Offered fetal structural ultrasound 18-22 wks

*Recommended in some populations
†Also called noninvasive prenatal screening (NIPS).

amniocenteses. Treatment is indicated primarily for maternal respiratory discomfort.

Oligohydramnios is associated with congenital anomalies; FGR; pre-eclampsia; severe [illegible] that interfere with fetal urination (see Table 116.6). Oligohydramnios becomes most evident after 16-20 weeks of gestation, when fetal urination is the major source of amniotic fluid. Premature rupture of membranes is a common cause of oligohydramnios and must be ruled out if present, especially if a normal-sized bladder and kidneys are seen on fetal ultrasound. Oligohydramnios causes fetal compression abnormalities such as fetal distress/stillbirth from umbilical cord compression, clubfoot, spadelike hands, and a flattened nasal bridge. The most serious complication of chronic oligohydramnios is **pulmonary hypoplasia**, especially if present during the canalicular stage of fetal lung development, which occurs between 16 and 24 weeks of gestation. The risk of umbilical cord compression during labor and delivery is increased in pregnancies complicated by oligohydramnios and may be alleviated by saline amnioinfusion via a transcervical intrauterine pressure catheter, which has been demonstrated to reduce the need for cesarean section and improve Apgar scores. The Society for Maternal Fetal Medicine suggests delivery decisions for oligohydramnios be made based on DVP <2 cm as opposed to AFI to limit interventions.

FGR is defined as an ultrasound-estimated fetal weight or abdominal circumference less than the 10th percentile for gestational age. It occurs in up to 10% of pregnancies and is a leading cause of neonatal morbidity and mortality. FGR increases the risk of stillbirth, acidosis at birth, low 5-minute Apgar, and neonatal intensive care unit admission. Concurrent preterm birth increases these risks. FGR also increases the risk of long-term morbidity. Children with a history of FGR are at increased risk of cardiovascular disease and remodeling, metabolic syndrome, and cognitive and learning disabilities.

The etiology of FGR is varied and can be a result of maternal, fetal, or placental conditions, but the unifying pathway is often placental dysfunction and poor fetal nutrition.

Early-onset FGR (diagnosed <32 weeks) is more likely to be associated with maternal hypertensive disease, fetal aneuploidy, or fetal infection

Table 116.6 Conditions Associated with Disorders of Amniotic Fluid Volume

OLIGOHYDRAMNIOS
Uteroplacental Insufficiency
Fetal growth restriction
Preeclampsia
Twin-twin transfusion (donor)
Placental abruption (chronic)
Arthrogryposis including fetal akinesia deformation syndrome
Other
Amniotic fluid leak/rupture of membranes
Fetal GU obstruction (e.g., bladder outlet obstruction)
Fetal renal failure (e.g., bilateral renal agenesis, multicystic dysplastic kidney)
Indomethacin
Angiotensin-converting enzyme inhibitors or receptor antagonists
POLYHYDRAMNIOS
Impaired Swallowing or Obstruction
Neuromuscular
CNS abnormalities
Arthrogryposis including fetal akinesia deformation syndrome
Spina bifida
GI Obstruction
Tracheoesophageal fistula
Intestinal atresia
Diaphragmatic hernia
Thoracic masses
Craniofacial
Cleft lip or palate
Micrognathia
Neck mass
EXCESSIVE URINE PRODUCTION
Renal/Urinary
Postobstructive diuresis (e.g., UPJ obstruction)
Bartter syndrome
Cardiac
Cardiac structural anomaly
Tachyarrhythmia
Sacrococcygeal teratoma
Chorangioma
Osmotic Diuresis/Other
Diabetes mellitus
Twin-twin transfusion (recipient)
Hydrops (immune or nonimmune)
Idiopathic

CNS, Central nervous system; GI, gastrointestinal; GU, genitourinary; UPJ, ureteropelvic junction.

(especially cytomegalovirus [CMV]), and tends to progress and become more severe. Late-onset FGR is more common (70–80%). Pregnancies with FGR, regardless of etiology, are high risk with an increased risk of stillbirth. These fetuses are serially monitored with growth ultrasound, NST/BPP, fluid assessment, and umbilical artery Doppler after fetal viability. Timing of delivery is dictated by severity of FGR and concurrent maternal-fetal conditions with delivery as early as 30-32 weeks recommended for FGR with reversed end-diastolic flow on umbilical artery Doppler.

LABOR AND DELIVERY

The rationale behind intrapartum **electronic fetal monitoring** (EFM) is that the fetal brain modulates FHR through sympathetic and parasympathetic input, and that characteristic changes in FHR indicate fetal hypoxia. Normal FHR patterns have a baseline between 110 and 160 beats/min, moderate variability (5-25 beats/min beat-to-beat variability), and an absence of FHR decelerations. When this pattern is not seen, the fetus may be at risk for hypoxia and acidosis. *Intrauterine resuscitative measures include lateral maternal positioning, intravenous fluids, tocolytic therapy (e.g., terbutaline), discontinuation of oxytocin, and amnioinfusion.* However, the effectiveness of EFM in reducing perinatal asphyxial injury is limited. Compared to intermittent auscultation, intrapartum EFM reduced the risk of neonatal seizures but failed to reduce perinatal mortality or cerebral palsy. EFM also increases the risk of cesarean delivery and operative delivery. Despite these limitations, EFM is the most common obstetric procedure with the vast majority of laboring people in the United States undergoing EFM.

Mode of delivery is influenced by a complex interplay between maternal-fetal factors. Spontaneous vaginal delivery is always preferred when not otherwise contraindicated. Approximately 20% of pregnancies in the United States, and a higher proportion of high-risk pregnancies, undergo induction of labor (IOL) with the goal of achieving a vaginal delivery. IOL is reasonable when the benefits of delivery (maternal or perinatal) outweigh the risks of continuing pregnancy. Even among low-risk pregnancies, IOL at 39 weeks appears to reduce maternal risks of cesarean birth and hypertensive disorders of pregnancy, whereas composite perinatal outcomes were unchanged with IOL compared to expectant management.

IOL often begins with cervical ripening, which functions like the cervical remodeling of physiologic parturition. Cervical ripening results in cervical softening and effacement, which reduces in the rate of failed induction and induction-to-delivery time. The most common cervical ripening agents are prostaglandin E analogs (e.g., misoprostol, dinoprostone) and mechanical cervical dilations, particularly balloon devices or foley catheters placed transcervically. These methods may be used alone or combined to facilitate cervical ripening, with combined methods resulting in faster time-to-delivery. Oxytocin infusion and amniotomy are the most common induction agents after cervical ripening has occurred.

Cesarean birth is indicated for a wide variety of circumstances. Infants born via cesarean may have complications related to the unfavorable obstetric circumstance that necessitated this mode of delivery. In normal term pregnancies, without indication of fetal distress, cesarean birth carries a greater neonatal risk than vaginal birth. Even when accounting for gestational age, malformations, birthweight, and multiple gestations, infants born ≥34 weeks of gestation via elective cesarean birth have 2 times the mortality rate of infants born following a planned vaginal birth, even if cesarean delivery was ultimately required. They also are 1.4 times as likely to require neonatal intensive care unit admission and 1.8 times as likely to require breathing support for >30 minutes after birth. Cesarean-born infants are also at increased risk for persistent pulmonary hypertension of the newborn. Any elective delivery, whether via IOL or cesarean, should be delayed until 39 weeks of gestation to reduce neonatal morbidity.

Operative vaginal birth with vacuum or forceps is a safe alternative to cesarean birth in appropriately selected patients. The absolute rate of significant newborn injury from these procedures is low, with rates ranging from 1 in 650-850 for **intracranial hemorrhage** and 1 in 220-385 for **neurologic complications**. With some of these injuries, the *indication* for operative vaginal birth is more likely to be associated with the injury than the procedure itself, and could not have been prevented with a cesarean birth.

Obstetric anesthesia is a vital component of care on the labor and delivery unit. The most common form of anesthesia in this patient population is *regional* (i.e., epidural or spinal). From the fetal/neonatal standpoint, the most significant complication encountered with this procedure is acute maternal hypotension, which can significantly impair uteroplacental perfusion. FHR abnormalities are common in this circumstance and, rarely, require emergent cesarean delivery if not amenable to standard in utero resuscitative efforts. *Opioid analgesia* is sometimes used in people who are not candidates for regional anesthesia. This form of pain relief is best avoided as delivery approaches to minimize risk of neonatal depression. To this end, when opioid use is necessary, it is best to prescribe regimens that have a very short half-life. It is essential that the pediatric team is present at the birth in people receiving opioid analgesia. Furthermore, the pediatricians must be alerted to the specific type of opioid used, because all these drugs cross the placenta and have varying neonatal pharmacokinetics.

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Chapter 117

The Fetus

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

The major emphasis in fetal medicine involves (1) assessment of fetal growth and maturity, (2) evaluation of fetal well-being or distress, (3) assessment of the effects of maternal disease on the fetus, (4) evaluation of the effects of drugs administered to the mother on the fetus, and (5) identification, and when possible, treatment of fetal disease or anomalies.

An important tool used to assess fetal well-being is ultrasonography (ultrasound [US]); it is both safe and reasonably accurate. Indications for antenatal US include estimation of gestational age (unknown dates, discrepancy between uterine size and dates, or suspected growth restriction), assessment of amniotic fluid volume, estimation of fetal weight and growth, determination of the location of the placenta and the number and position of fetuses, and identification of congenital anomalies. Fetal MRI is a more advanced imaging method that is thought to be safe for the fetus and neonate and is used for more advanced diagnostic and therapeutic planning (Fig. 117.1).

117.1 Fetal Growth and Maturity

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

Fetal growth can be assessed by US as early as 6-8 weeks of gestation by measurement of the crown-rump length. Accurate determination of gestational age can be achieved through the first half of pregnancy; however, first-trimester assessment by crown-rump length measurement is the most effective method of pregnancy dating. In the second trimester and beyond, a combination of biometric measures (i.e., biparietal diameter, head and abdominal circumference, femoral diaphysis length) is used for gestational age and growth assessment (Fig. 117.2). If a single US examination is performed, the most information can be obtained with a scan at 18-20 weeks, when both gestational age and fetal anatomy can be evaluated. Serial scans assessing fetal growth are performed when risk factors for **fetal growth restriction (FGR)** are present. Two patterns of FGR have been identified: *symmetric* FGR, typically present early in pregnancy, and *asymmetric* FGR, typically occurring later in gestation. The most widely accepted definition of FGR in the United States is an **estimated fetal weight (EFW)** of less than the 10th percentile (Fig. 117.3).

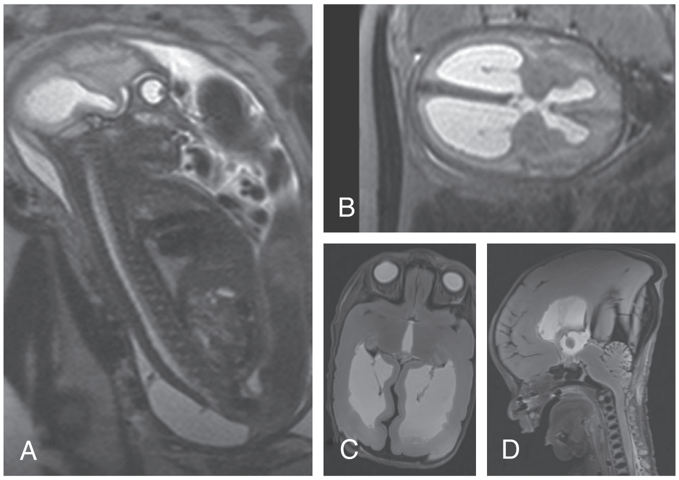

Fig. 117.1 MRI of fetal pathology. A, Fetus with sacral myelomeningocele at 30 weeks' gestation. B, Ventriculomegaly in the same fetus as in A. C, MRI can also be used for postmortem examination, here in a 33-week-old fetus, demonstrating ventriculomegaly with heterotopic foci in the ventricular walls. D, Chiari II malformation of the brainstem. (*Courtesy Filip Claus, Aalst, Belgium.*)

Fetal maturity and dating are usually assessed by last menstrual period (LMP), assisted reproductive technology (ART)–derived gestational age, or US assessments. Dating by LMP assumes an accurate recall of the first day of LMP, a menstrual cycle that lasted 28 days, and ovulation occurring on the 14th day of the cycle, which would place the **estimated delivery date (EDD)** 280 days after LMP. Inaccuracies with any of these parameters can lead to an incorrectly assigned gestational age if the LMP is used for dating. Dating by ART is the most accurate method for assigning gestational age with EDD occurring 266 days after conception (when egg is fertilized by sperm). When US is used for dating, the most accurate assessment of gestational age is by first-trimester (≤13 6/7 week) US measurement of crown-rump length, which is accurate to within 5-7 days. In contrast, US dating in the second trimester is accurate to 10-14 days, and third trimester is only accurate to 21-30 days. Dating of a pregnancy is critical to determine when delivery should occur, if growth is appropriate during the pregnancy, and when testing and interventions should be offered. The earliest assessment of pregnancy dating should be used throughout the pregnancy unless methodologies used later in pregnancy are significantly different.

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117.2 Fetal Distress

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

Fetal compromise may occur during the antepartum or intrapartum period. It may be asymptomatic in the antenatal period but is often suspected by maternal perception of decreased fetal movement. **Antepartum fetal surveillance** is warranted for women at increased risk for fetal death, including those with a history of stillbirth, intrauterine growth restriction (IUGR), oligohydramnios or polyhydramnios, multiple gestation, rhesus sensitization, hypertensive disorders, diabetes mellitus or other chronic maternal disease, decreased fetal movement, preterm labor, preterm rupture of membranes (PROM), and post term pregnancy. The predominant cause of antepartum fetal distress is uteroplacental insufficiency, which may manifest clinically as IUGR, fetal hypoxia, increased vascular resistance in fetal blood vessels (Figs. 117.4 and 117.5), and, when severe, mixed fetal respiratory and metabolic (lactic) acidosis. The goal of antepartum fetal surveillance is to identify the fetus at risk of stillbirth such that appropriate interventions (i.e., delivery vs optimization of underlying maternal medical condition) can be implemented to allow for a healthy liveborn infant. Table 117.1 lists methods for assessing fetal well-being.

The most common noninvasive tests are the nonstress test **(NST)** and the biophysical profile **(BPP)**. The NST monitors the presence of fetal heart rate **(FHR)** accelerations that follow fetal movement. A reactive (normal) NST result demonstrates two FHR accelerations of at least 15 beats/min above the baseline FHR lasting 15 seconds during 20 minutes of monitoring. A nonreactive NST result suggests possible fetal compromise and requires further assessment with a BPP. Although the NST has a low false-negative rate, it does have a high false-positive rate, which is often remedied by the BPP. The full BPP assesses fetal breathing, body movement, tone, NST, and amniotic fluid volume. It effectively combines acute and chronic indicators of fetal well-being, which improves the predictive value of abnormal testing (Table 117.2). A score of 2 or 0 is given for each observation. A total score of 8-10

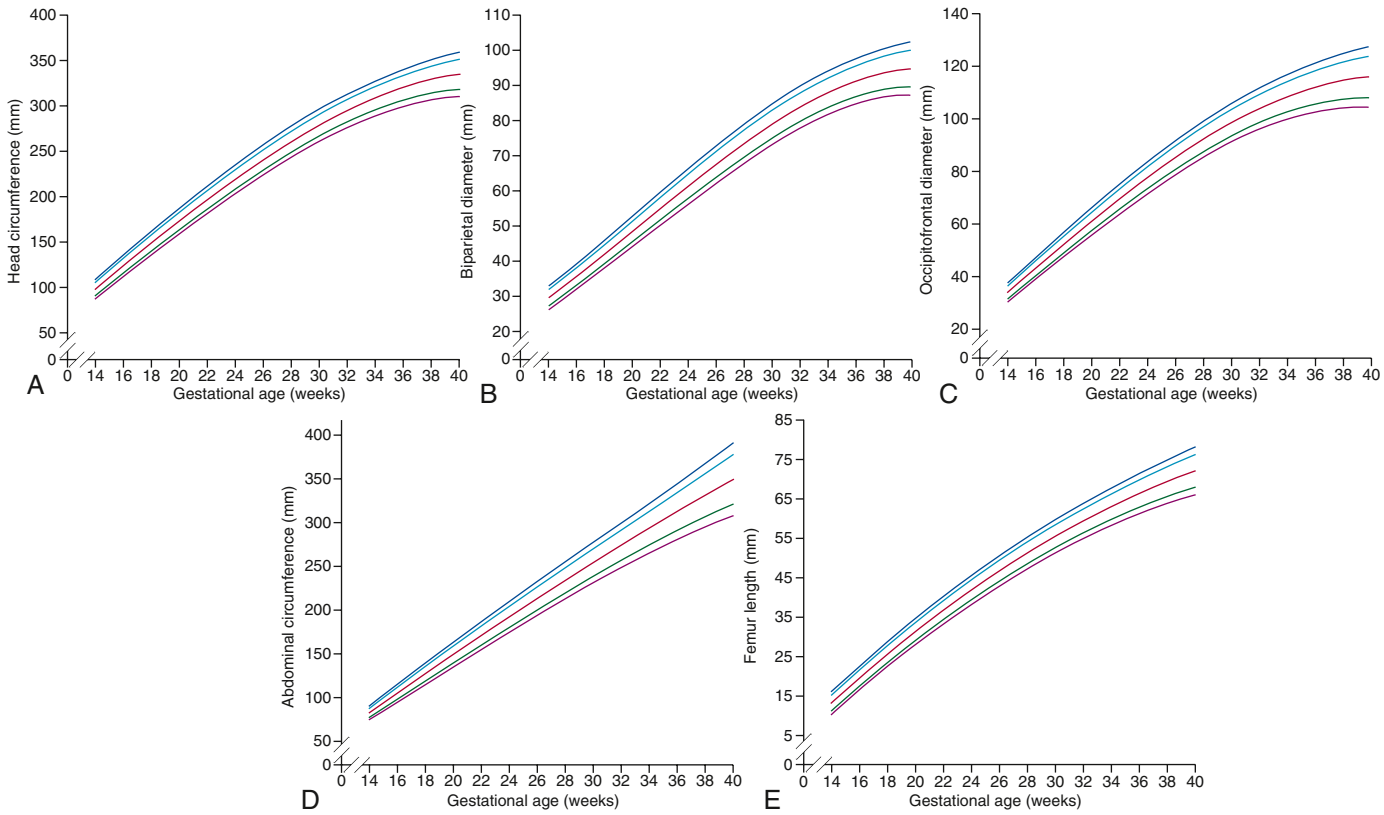

Fig. 117.2 Fetal measurements: 3rd, 10th, 50th, 90th, and 97th smoothed centile curves. **A,** Fetal head circumference. **B,** Fetal biparietal diameter. **C,** Fetal occipitofrontal diameter. **D,** Fetal abdominal circumference. **E,** Fetal femur length measured by ultrasound according to gestational age. (*From Papageorghiou AT, Ohyma EO, Altman DG, et al. International standards for fetal growth based on serial US measurements: The Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014;384:869–878. Fig. 3.*)

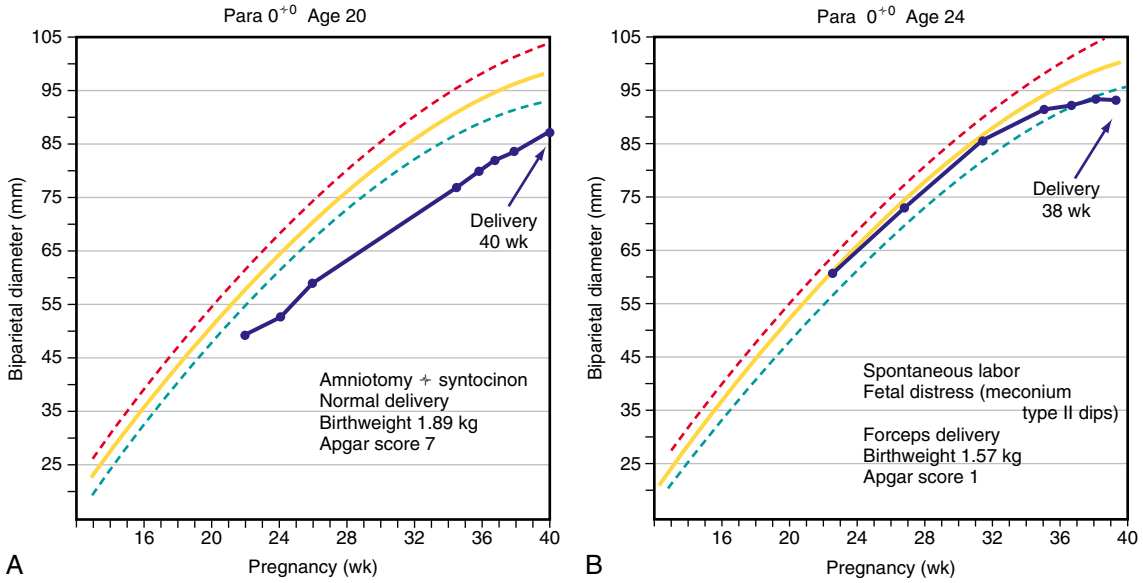

Fig. 117.3 **A,** Example of a "low-profile" growth restriction pattern in an uneventful pregnancy and labor. The baby cried at 1 minute, and hypoglycemia did not develop. Birthweight was below the 5th percentile for gestational age. **B,** Example of a "late-flattening" growth restriction pattern. The mother had a typical history of preeclampsia, and the infant had intrapartum fetal distress, a low Apgar score, and postnatal hypoglycemia. Birthweight was below the 5th percentile for gestational age. *Dashed green line*, 5th percentile; *solid yellow line*, 50th percentile; *dashed red line*, 95th percentile. (*From Campbell S. Fetal growth. Clin Obstet Gynecol. 1974;1:41–65.*)

is reassuring; a score of 6 is equivocal, and retesting should be done in 12-24 hours; and a score of 4 or less warrants immediate evaluation and possible delivery. The BPP has good negative predictive value. The modified BPP consists of the combination of an US estimate of amniotic fluid volume (the amniotic fluid index) and the NST. When results of both are normal, fetal compromise is very unlikely. Signs of progressive compromise seen on Doppler US include reduced, absent, or reversed diastolic waveform velocity in the fetal aorta or umbilical

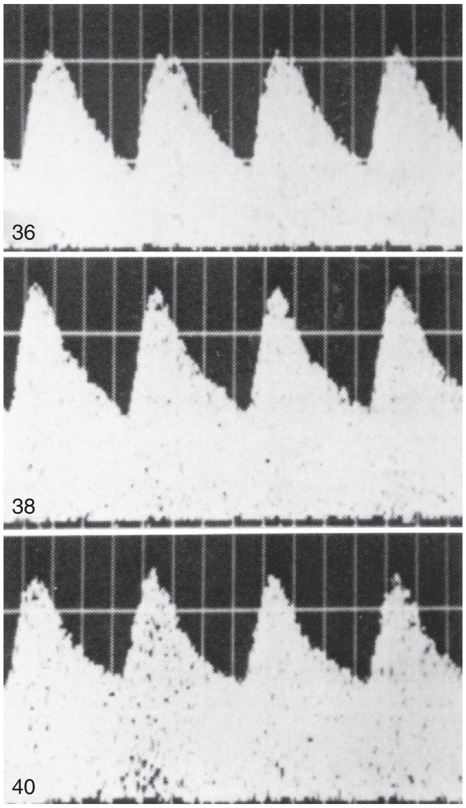

Fig. 117.4 Normal Doppler velocity in sequential studies of fetal umbilical artery flow velocity waveforms from one normal pregnancy. Note the systolic peak flow with lower but constant heart flow during diastole. The systolic/diastolic ratio can be determined and, in normal pregnancies, is <3 after the 30th week of gestation. The numbers indicate the weeks of gestation. (*From Trudinger B. Doppler US assessment of blood flow. In Creasy RK, Resnik R, eds. Maternal-Fetal Medicine: Principles and Practice. 5th ed. Philadelphia: Saunders; 2004.*)

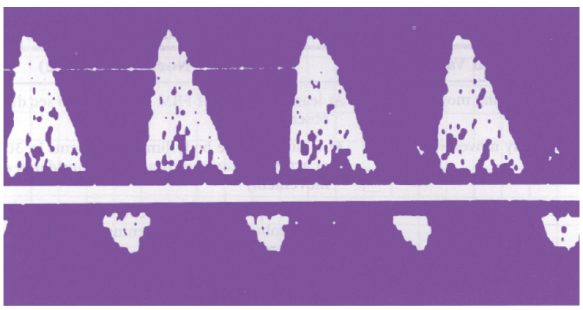

Fig. 117.5 Abnormal umbilical artery Doppler in which the diastolic component shows flow in a reverse direction. This finding occurs in severe intrauterine hypoxia and intrauterine growth restriction (*From Trudinger C. Doppler US assessment of blood flow. In: Creasy RK, Resnik R, eds. Maternal-Fetal Medicine: Principles and Practice. 5th ed. Philadelphia: Saunders; 2004.*)

artery (see Fig. 117.5 and Table 117.1). The umbilical vein and ductus venosus waveforms are also used to assess the degree of fetal compromise. Fetuses at highest risk of stillbirth often have combinations of abnormalities, such as growth restriction, oligohydramnios, reversed diastolic Doppler umbilical artery blood flow velocity, and a low BPP.

Fetal compromise *during labor* may be detected by monitoring the FHR, uterine pressure, and fetal scalp blood pH (Fig. 117.6). **Continuous fetal heart rate monitoring** detects abnormal cardiac patterns by instruments that compute the beat-to-beat FHR from a fetal electrocardiographic signal. Signals are derived either from an electrode attached to the fetal presenting part, from an ultrasonic transducer placed on the maternal abdominal wall to detect continuous ultrasonic waves reflected from the contractions of the fetal heart, or from a phonotransducer placed on the mother's abdomen. Uterine contractions are recorded from an intrauterine pressure catheter or from an external tocotransducer applied to the maternal abdominal wall overlying the uterus. FHR patterns show various characteristics, some of which suggest fetal compromise. The baseline FHR is determined over 10 minutes devoid of accelerations or decelerations. Over the course of pregnancy, the normal baseline FHR gradually decreases from approximately 155 beats/min in early pregnancy to 135 beats/min at term. The normal range throughout pregnancy is 110-160 beats/min. **Tachycardia** (>160 beats/min) is associated with early fetal hypoxia, maternal fever, maternal hyperthyroidism, maternal β-sympathomimetic drug or atropine therapy, fetal anemia, infection, and some fetal arrhythmias. Arrhythmias do not generally occur with congenital heart disease and may resolve spontaneously at birth. **Fetal bradycardia** (<110 beats/min) may be normal (e.g., 105-110 beats/min) but may occur with fetal hypoxia, placental transfer of local anesthetic agents and β-adrenergic blocking agents, and occasionally, heart block with or without congenital heart disease.

Normally, the baseline FHR is variable as a result of opposing forces from the fetal sympathetic and parasympathetic nervous systems. **Variability** is classified as follows: *absence of variability,* if an amplitude change is undetectable; *minimal* variability, if amplitude range is ≤5 beats/min; *moderate* variability, if amplitude range is 6-25 beats/min; and *marked* variability, if amplitude range is >25 beats/min. Variability may be decreased or lost with fetal hypoxemia or the placental transfer of drugs such as atropine, diazepam, promethazine, magnesium sulfate, and most sedative and narcotic agents. Prematurity, the sleep state, and fetal tachycardia may also diminish beat-to-beat variability.

Accelerations or decelerations of the FHR in response to or independent of uterine contractions may also be monitored (see Fig. 117.6). An **acceleration** is an abrupt increase in FHR of ≥15 beats/min in ≥15 seconds. The presence of accelerations or moderate variability reliably predicts the absence of fetal metabolic acidemia. However, their absence does not reliably predict fetal acidemia or hypoxemia. **Early decelerations** are a physiologic vagal response to uterine contractions, with resultant fetal head compression, and represent a repetitive pattern of gradual decrease and return of the FHR that is coincidental with the uterine contraction (Table 117.3). **Variable decelerations** are associated with umbilical cord compression and are characterized by a V-shaped or U-shaped pattern, are abrupt in onset and resolution, and may occur with or without uterine contractions.

Late decelerations are associated with fetal hypoxemia and are characterized by onset after a uterine contraction is well established and persists into the interval following resolution of the contraction. The late deceleration pattern is usually associated with maternal hypotension or excessive uterine activity, but it may be a response to any maternal, placental, umbilical cord, or fetal factor that limits effective oxygenation of the fetus. The significance of late decelerations varies according to the underlying clinical context. They are most likely to be associated with true fetal hypoxemia/acidemia when they are recurrent and occur in conjunction with decreased or absent variability. Late decelerations represent a compensatory, chemoreceptor-mediated response to fetal hypoxemia. The transient decrease in FHR serves to increase ventricular preload during the peak of hypoxemia (i.e., at the crest of a uterine contraction). If fetal acidemia progresses, late decelerations may become less pronounced or absent, indicating severe hypoxic depression of myocardial function. Prompt delivery is indicated if late decelerations are unresponsive to oxygen supplementation, hydration, discontinuation of labor stimulation, and position changes. Approximately 10–15% of term fetuses have *terminal* (just before delivery) FHR decelerations that are usually benign if they last <10 minutes before delivery.

A three-tier system has been developed by a panel of experts for interpretation of FHR tracings (Table 117.4). **Category I tracings** are normal and are strongly predictive of normal fetal acid-base status at

Table 117.1 Fetal Diagnosis and Assessment

METHOD	COMMENT(S) AND INDICATION(S)
IMAGING	
Ultrasound (real-time)	Biometry (growth), anomaly detection (including congenital heart disease, GI, CNS, skeletal), number of fetuses, sites of calcification
	Biophysical profile
	Amniotic fluid volume, hydrops
Ultrasound (Doppler)	Velocimetry (blood flow velocity)
	Detection of increased vascular resistance in the umbilical artery secondary to placental insufficiency
	Detection of fetal anemia (MCA Doppler)
MRI	Defining of lesions before fetal surgery
	Better delineation of fetal CNS anatomy
FLUID ANALYSIS	
Amniocentesis	Karyotype or microarray (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, or α-fetoprotein determination
	Bacterial culture, pathogen antigen, or genome detection (PCR)
Cordocentesis (percutaneous umbilical blood sampling)	Detection of blood type, anemia, hemoglobinopathies, thrombocytopenia, polycythemia, acidosis, hypoxia, thrombocytopenia, IgM antibody response to infection
	Rapid karyotyping and molecular DNA genetic diagnosis
	Fetal therapy (see Table 117.9)
FETAL TISSUE ANALYSIS	
Chorionic villus biopsy	Cytogenetic and molecular DNA analysis, enzyme assays
Circulating fetal DNA (cell free DNA)*	Noninvasive molecular DNA genetic analysis including microarray analysis and chromosome number (screening method)
MATERNAL SERUM α-FETOPROTEIN CONCENTRATION	
Elevated	Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis, nephrosis, fetal demise, incorrect gestational age
Reduced	Trisomies, aneuploidy
MATERNAL CERVIX	
Fetal fibronectin	Indicates possible risk of preterm birth
Transvaginal cervical length	Short length suggests possible risk of preterm birth
Bacterial culture	Identifies risk of neonatal infection (group B streptococcus, *Neisseria gonorrhoeae, Chlamydia trachomatis*)
Amniotic fluid	Determination of PROM
ANTEPARTUM BIOPHYSICAL MONITORING	
Nonstress test	Fetal distress; hypoxia
Biophysical profile and modified biophysical profile	Fetal distress; hypoxia
Intrapartum fetal heart rate monitoring	See Fig. 117.6

GI, Gastrointestinal; CNS, central nervous system; MCA, middle cerebral artery; PCR, polymerase chain reaction; PROM, premature rupture of membranes.
*Maternal circulation.

Table 117.2 Biophysical Profile Scoring: Technique and Interpretation

BIOPHYSICAL VARIABLE	NORMAL SCORE (2)	ABNORMAL SCORE (0)
Fetal breathing movements (FBMs)	At least one episode of FBM of at least 30 sec duration in 30 min observation	Absence of FBM or no episode ≥30 sec in 30 min
Gross body movement	At least three discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)	Two or fewer episodes of body/limb movements in 30 min
Fetal tone	At least one episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection
Reactive fetal heart rate (FHR)	At least two episodes of FHR acceleration of ≤15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min	Less than two episodes of acceleration of FHR or acceleration of <15 beats/min in 30 min
Quantitative amniotic fluid (AF) volume*	At least one pocket of AF that measures at least 2 cm in two perpendicular planes	Either no AF pockets or a pocket <2 cm in two perpendicular planes

*Modification of the criteria for reduced amniotic fluid from <1 cm to <2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.
From Creasy RK, Resnik R, Iams JD, eds. *Maternal-Fetal Medicine: Principles and Practice.* 5th ed. Philadelphia: Saunders; 2004.

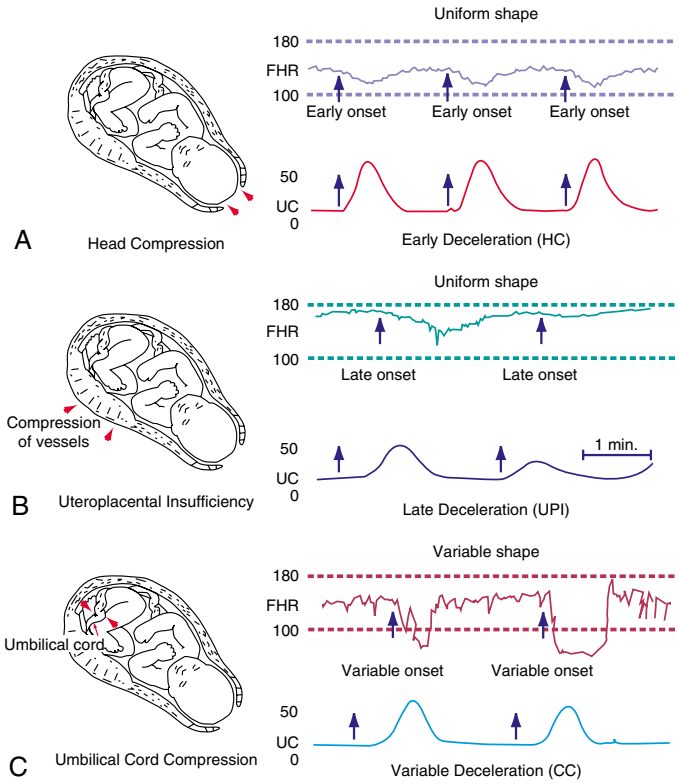

Fig. 117.6 Patterns of periodic fetal heart rate (FHR) deceleration. The tracing in A shows early deceleration occurring during the peak of uterine contractions (UC) as a result of pressure on the fetal head. B, Late deceleration caused by uteroplacental insufficiency (UPI). C, Variable deceleration as a result of umbilical cord compression. *Arrows* denote the time relationship between the onset of FHR changes and uterine contractions. (*From Hon EH. An Atlas of Fetal Heart Rate Patterns. New Haven, CT: Harty Press; 1968.*)

Table 117.3 Characteristics of Decelerations of Fetal Heart Rate (FHR)

LATE DECELERATION
• Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction.
• A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the nadir of the FHR.
• The decrease in FHR is calculated from the onset to the nadir of the deceleration.
• The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
• In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.
EARLY DECELERATION
• Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction.
• A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the FHR nadir.
• The decrease in FHR is calculated from the onset to the nadir of the deceleration.
• The nadir of the deceleration occurs at the same time as the peak of the contraction.
• In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.
VARIABLE DECELERATION
• Visually apparent, *abrupt* decrease in FHR.
• An *abrupt* FHR decrease is defined as duration <30 sec from the onset of the deceleration to the beginning of the FHR nadir of the deceleration.
• The decrease in FHR is calculated from the onset to the nadir of the deceleration.
• The decrease in FHR is ≥15 beats/min, lasting ≥15 sec, and <2 min in duration.
• When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

From Macones GA, Hankins GDV, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol.* 2008;112:661–666.

the time of the observation. **Category II tracings** are not predictive of abnormal fetal status, but there is insufficient evidence to categorize them as category I or III; therefore further evaluation, surveillance, and reevaluation are indicated. **Category III tracings** are abnormal and predictive of abnormal fetal acid-base status at the time of observation. Category III tracings require prompt evaluation and efforts to resolve expeditiously the abnormal FHR as previously discussed for late decelerations.

Umbilical cord blood samples obtained at delivery are useful to document fetal acid-base status. Although the exact cord blood pH value that defines significant fetal acidemia is unknown, an umbilical artery pH <7.0 has been associated with greater need for resuscitation and a higher incidence of respiratory, gastrointestinal, cardiovascular, and neurologic complications. Nonetheless, in many cases, even when a low pH is detected, newborn infants are neurologically normal.

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117.3 Maternal Disease and the Fetus

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INFECTIOUS DISEASES

See Table 116.3 for a list of common maternal infectious diseases that impact the fetus and newborn.

Almost any maternal infection with severe systemic manifestations may result in miscarriage, stillbirth, or premature labor. Whether these results are a consequence of infection of the fetus or are secondary to maternal illness is not always clear. Another important factor to consider when dealing with infectious diseases in pregnancy is the timing of infection. In general, infections that occur earlier in the pregnancy (first or second trimester) are more likely to result in miscarriage or problems with organogenesis, such as the neuromigrational abnormalities seen in newborns with congenital cytomegalovirus (CMV) infections.

Cytomegalovirus (CMV) is the most common congenital infection, affecting 0.2–2.2% of all neonates (see Chapter 302). Perinatal transmission can occur at any time during the pregnancy; however, the most devastating sequelae occur with first-trimester infection. After a primary infection, 12–18% of neonates will have signs and symptoms at birth, and as many as 25% can develop long-term complications. The most common complication is **congenital hearing loss**. Severely affected infants have an associated 30% mortality, and 65–80% of survivors develop severe neurologic morbidity. A mother with a history of CMV may experience reactivation of the disease or may be infected with a different strain of the virus and transmit the infection to the fetus. Currently, there are no well-studied or validated antenatal therapies targeted toward decreasing disease severity or preventing congenital infection in the setting of primary maternal CMV infection. Preliminary data from some studies have demonstrated promise with drugs such as valganciclovir and CMV-specific hyperimmune globulin, but confirmatory data are lacking. For this reason, the American College of Obstetricians and Gynecologists (ACOG) does not recommend

Table 117.4 Three-Tier Fetal Heart Rate (FHR) Interpretation System

CATEGORY I

Category I FHR tracings include all the following:
- Baseline rate: 110-160 beats/min
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

CATEGORY II
- Category II FHR tracings include all FHR tracings not categorized as category I or category III.
- Category II tracings may represent an appreciable fraction of those encountered in clinical care.
- Examples of category II FHR tracings include any of the following.

Baseline Rate
- Bradycardia not accompanied by absence of baseline variability
- Tachycardia

Baseline FHR Variability
- Minimal baseline variability
- Absence of baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations
- Absence of induced accelerations after fetal stimulation

Periodic or Episodic Decelerations
- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration, ≥2 min but <10 min
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," and "shoulders"

CATEGORY III

Category III FHR tracings include either:
- Absence of baseline FHR variability

OR

Any of the following:
- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia
- Sinusoidal pattern

Adapted from Macones GA, Hankins GDV, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol.* 2008;112:661–666.

antenatal therapy for congenital CMV infection outside of an established research protocol.

During the **COVID-19** pandemic, all pregnant persons admitted to the hospital were screened for the severe acute respiratory syndrome virus 2 (SARS-CoV-2) by polymerase chain reaction (PCR) testing on a sample obtained by a nasopharyngeal swab (see Chapter 311). Symptomatic maternal COVID-19 has been associated with maternal mortality, higher rate of C-section delivery, preeclampsia, and preterm birth; ~50% of the women are asymptomatic. Among symptomatic mothers, most had mild to moderate symptoms such as cough and fever, but 5% had severe symptoms requiring ICU admission. The majority of neonates born to these mothers are full-term; 15% were born before 37 weeks, and 5% were born before 32 weeks. The rates of preterm birth are threefold higher compared to baseline. Only a minority of infants will require neonatal resuscitation. About 19% of the infants will be admitted to the NICU for symptoms including those of prematurity. Only ~3% will test positive by initial nasopharyngeal swab done within the first 12 hours of life. Among infants who test positive, all remain asymptomatic except for those with respiratory distress from prematurity. Importantly, in ~50% of cases, delayed cord clamping, rooming-in, and breastfeeding can be achieved with standard precautions without adverse effects. The WHO recommends routine newborn care with infection control precautions, whereas the CDC encourages shared decision-making. Current evidence suggests that vertical transmission of the virus during pregnancy is unlikely, and neonatal symptomatic infection uncommon.

NONINFECTIOUS DISEASES (SEE TABLE 116.2)

Maternal diabetes increases the risk for neonatal hypoglycemia, hypocalcemia, respiratory distress syndrome and other respiratory problems, feeding difficulties, polycythemia, macrosomia, growth restriction (with severe vascular/renal disease), myocardial dysfunction, jaundice, and congenital malformations (see Chapter 147). There is an increased risk of uteroplacental insufficiency, polyhydramnios, and fetal demise in poorly controlled diabetic mothers. **Preeclampsia-eclampsia**, **chronic hypertension**, and **chronic renal disease** can result in IUGR, prematurity, and fetal death, all probably caused by diminished uteroplacental perfusion.

Uncontrolled maternal **hypothyroidism** or **hyperthyroidism** can lead to relative infertility, spontaneous abortion, premature labor, preeclampsia, placental abruption, and fetal death. Maternal screening for thyroid disease is recommended for women at risk, such as those with a history of thyroid disease or medical conditions associated with thyroid disease. Measuring maternal thyroid-stimulating hormone (TSH) levels is an accurate way of assessing thyroid function provided trimester-specific cutoffs are used for interpretation as TSH levels decline in the first trimester. Similarly, total T_3 and T_4 levels increase with pregnancy and the upper limits of these levels are 1.5 times those in nonpregnant persons. Hyperthyroidism during pregnancy can be diagnosed by a low TSH level and a corresponding increase in free T_3/T_4 or both.

Graves disease is the most common cause of hyperthyroidism during pregnancy. In maternal Graves disease, TSH receptor antibodies (TRAb) are present and can cross the placenta as these are IgG antibodies. There are two types of TRAb antibodies, stimulating and blocking. TRAb stimulating antibodies can bind to the TSH receptor on the thyroid follicular cells in the fetus and cause autonomous thyroid hormone production, whereas the blocking antibodies do not lead to thyroid hormone production. TRAb stimulating antibodies can lead to in utero or neonatal hyperthyroidism. In the fetus, symptoms usually develop in the third trimester. Although uncommon, fetal hyperthyroidism can lead to fetal tachycardia, nonimmune hydrops from heart failure, preterm birth, advanced skeletal maturation, and craniosynostosis. Graves disease during pregnancy can be treated with propylthiouracil. Rarely, a thyroidectomy may be required. Neonatal hyperthyroidism can present with a variety of symptoms including goiter, low birthweight, exophthalmos, hyperthermia, irritability, fatigue, diarrhea, poor weight gain, tachycardia, hypertension, heart failure, hepatosplenomegaly, or thrombocytopenia. These symptoms can be confused with sepsis or congenital viral infections; therefore a high index of suspicion is necessary. Symptomatic neonates can be treated with an antithyroid agent such as methimazole. Sympathetic symptoms can be treated with β blockers such as propranolol. Typically, treatment is required for 1-2 months, until circulating antibodies are present.

Similarly, maternal hypothyroidism can be diagnosed by an elevated TSH level with a decreased free T_4. The most common cause of hypothyroidism in pregnancy is chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Hypothyroidism is treated with levothyroxine with the goal of normalizing maternal TSH levels. Maternal euthyroid status is very important for fetal growth, specifically fetal brain growth, because for the first half of pregnancy the fetus is dependent on maternal thyroid hormone for development. Therefore maternal hypothyroidism can lead to poor fetal neurodevelopment and lower IQ in children. Normalization of maternal thyroid hormone levels can prevent adverse neurodevelopmental outcomes.

Maternal **immunologic diseases** such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, and Graves disease, all of which are mediated by immunoglobulin G

Table 117.5 Factors Known To Be Associated with or Causative for Stillbirth

MATERNAL FACTORS
• Black ethnicity
• Low socioeconomic status
• Prior history of stillbirth
• Smoking
• Hypertensive disorders
• Diabetes
• Advanced maternal age
• Obesity
• Maternal anemia/polycythemia
• Thyroid disorders (both hypo- and hyperthyroidism)
• Systemic lupus erythematosus
• Chronic renal disease
• Prescription pain medications
• Substance use disorders including alcohol
• Residential and occupational toxin exposure
• Thrombophilias including antiphospholipid antibodies
• Maternal trauma
• Maternal infections
FETAL FACTORS
• Congenital anomalies (usually caused by major chromosomal abnormalities)
• Infections
• Multiple gestation (twin-twin transfusion syndrome and monoamniotic twinning)
• Fetal growth restriction
• Metabolic disorders (hemoglobinopathies, glycogen storage disorders, aminoacidurias, peroxidase deficiencies)
• Immune and nonimmune hydrops
DELIVERY FACTORS
• Post dates
• Placental abruption
• Umbilical cord accidents

Data from RL Goldenberg, Kirby R, Culhane JF. Stillbirth: A review. *J Matern.-Fetal Neonatal Med.* 2004;16:79–94. Available from https://www.tandfonline.com/doi/abs/10.1080/jmf.16.2.79.94

autoantibodies that can cross the placenta, frequently cause transient illness in the newborn. Maternal autoantibodies to the folate receptor are associated with neural tube defects **(NTDs)**, whereas maternal immunologic sensitization to fetal antigens may be associated with neonatal alloimmune hepatitis and neonatal alloimmune thrombocytopenia **(NAIT)**.

Untreated metabolic disorders such as maternal **phenylketonuria** (PKU) results in miscarriage, congenital cardiac malformations, and injury to the brain of a nonphenylketonuric heterozygous fetus. Women whose PKU is well controlled before conception can avoid these complications and have a normal newborn.

STILLBIRTH

Stillbirth is defined as the loss of a fetus before or during the process of delivery, usually after 20 weeks of pregnancy, or when gestational age is unknown, at a birthweight >350 g. Stillbirths can be antenatal (when they are typically referred to as intrauterine fetal demise [IUFD]), or intrapartum. In the United States, the rates of stillbirth are about 7 per 1,000 live births. There has been a dramatic decline in the rates of stillbirth since the 1960s largely attributed to the administration of Rh immune globulin. In addition, improved antenatal and intrapartum fetal monitoring, better control of maternal medical conditions such as diabetes, and early detection of congenital anomalies has also contributed to the decrease in stillbirth rates.

Factors associated with stillbirth are listed in Table 117.5. Among all causes of stillbirths, maternal infections account for 25% of cases, followed by growth restriction and placental causes in about 20% of cases, followed by maternal hypertensive disorders, and then congenital anomalies and cord accidents.

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117.4 Medications and Teratogenic Exposures

Sonja A. Rasmussen

When a child has a birth defect or developmental delay, parents often worry about whether the problem is due to something they did during the pregnancy. The pediatrician needs to be able to evaluate exposures to infections, prescription and over-the-counter medications as well as illegal drugs and alcohol, occupational chemicals, and other possible reproductive hazards to help parents understand potential causes of their child's birth defects and, when necessary, educate parents about how to avoid hazardous exposures in future pregnancies. In many cases the pediatrician can reassure the family that there is nothing they did or did not do to cause their child's problems.

A **teratogenic exposure (reproductive hazard)** is defined as an exposure during pregnancy that increases the risk of pregnancy loss, congenital malformation or functional impairment, such as developmental delay. Teratogenic exposures include medications (e.g., thalidomide or isotretinoin), infections (e.g., rubella, CMV, or Zika virus), physical agents (e.g., radiation), recreational exposures (e.g., alcohol or smoking), maternal conditions (e.g., pregestational diabetes, hyperthermia, or maternal PKU), and environmental chemicals (e.g., lead or mercury). An excellent internet-based resource called **MotherToBaby** (mothertobaby.org) provides comprehensive and routinely updated summaries on commonly used medications and other potentially teratogenic exposures in pregnancy, as well as free consultation with experts regarding pregnancy exposures. Other resources include TERIS (http://depts.washington.edu/teriswebb/teris/) and Reprotox (www.reprotox.org), which both require a subscription.

In at least 50% of cases, the causes of birth defects are unknown. Overall, less than 5% of anomalies noted at birth are caused by recognized teratogenic exposures. Although relatively few agents are recognized to be teratogenic in humans, new agents continue to be identified. In 2016, Zika virus infection during pregnancy was identified as a new cause of birth defects after a large outbreak of Zika virus in Brazil led to a dramatic increase in the number of infants born with microcephaly and other serious birth defects, known as the congenital Zika syndrome.

Teratogenic exposures often produce a certain type of defect or a characteristic pattern of malformations. Many factors modify the effects of teratogenic exposures. The timing of exposure is critical; exposures during embryogenesis (2-8 weeks of gestation) are most likely to cause congenital malformations, but exposures later in pregnancy can also be detrimental. For example, second- and third-trimester exposure to antihypertensive medications that inhibit the renin-angiotensin system, particularly angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, results in decreased fetal renal function, which can cause oligohydramnios, growth deficiency, pulmonary hypoplasia, hypocalvaria, renal dysplasia, and death. Dose is also important. Some agents have a dose or **threshold effect**, below which no alterations in growth, function, or structure occur. The effects of exposure to radiation emphasize the importance of dose; high doses of radiation exposure (e.g., in the aftermath of the atomic bombs in Hiroshima and Nagasaki) during pregnancy caused increases in the risks for pregnancy loss, congenital malformations, neurobehavioral effects, and growth restriction. These outcomes appear to have a threshold effect; that is, below a certain threshold, no effects occur. With few exceptions, the level of radiation exposure associated with diagnostic radiologic studies is not expected to exceed this threshold. This has led expert groups such as the ACOG to state that if these procedures are needed, they should not be withheld from a pregnant person. The genetic makeup of the mother and fetus are also important; genetic variants can affect the metabolism of potential teratogens and increase or decrease their teratogenic risk. In many

circumstances the same agent and dose may not consistently produce the adverse outcome in different pregnancies.

Although much of the focus has been on exposures that increase the risk of birth defects, certain exposures can decrease the risk. For example, **folic acid** fortification of cereal-grain products, which became mandatory in the United States in 1998, and oral folic acid tablets or multivitamins containing folic acid are associated with a reduced birth prevalence of NTDs and perhaps other birth defects. Folic acid fortification of cereal-grain products in the United States has resulted in more than 1,300 fewer births a year affected by NTDs. All women who are planning or capable of pregnancy are recommended to take a daily supplement containing 0.4-0.8 mg of folic acid.

In 2015, the U.S. Food and Drug Administration (FDA) put into effect the Pregnancy and Lactation Labeling Final Rule, which replaced its previous classification of prescription medications into five pregnancy risk categories (categories A, B, C, D, and X) with a new narrative format. The current label includes narrative sections to include information on pregnancy, lactation, and the effects on females and males of reproductive potential. The pregnancy section includes information on pregnancy exposure registries, a risk summary, clinical considerations, and data.

The use of certain medications during pregnancy is potentially harmful to the fetus. Exposure to multiple medications occurs in the majority of pregnancies, with gastrointestinal medications, antibiotics, and analgesics making up the most commonly used medication classes. About 30% of women report taking at least five medications during pregnancy. Unfortunately, for over 90% of drugs recently approved by the FDA, the teratogenic risk is undetermined. Moreover, many women are exposed to potential reproductive toxins, such as occupational, environmental, or household chemicals.

Spontaneous abortions or **birth defects** can result from the maternal ingestion of teratogenic medications during the period of organogenesis. Maternal medications taken later, particularly during the last few weeks of gestation or during labor, more often affect the function of specific organs or enzyme systems to adversely affect the neonate rather than the fetus. Not all adverse outcomes from teratogenic exposures are evident immediately in the delivery room. Some, like cognitive impairments, are not noted until the child is older, and others may not be evident until later in life. For example, the administration of diethylstilbestrol (DES) during pregnancy increased the risk for vaginal and cervical clear cell adenocarcinoma in female offspring in the second or third decade of life.

The importance of controlling maternal disease must be balanced with the risk of possible complications from treatment to the fetus. Most newborns born to women with epilepsy are born without congenital malformation. Nonetheless, several commonly used **antiepileptic drugs** are associated with an increased risk for birth defects. Data comparing different antiepileptic treatments have shown that valproate is associated with the highest risk (over 10% of infants born after maternal exposure in the first trimester to valproate had congenital malformations), with the lowest risk for lamotrigine. Infants exposed to **valproic acid** may have multiple types of anomalies, including NTDs, congenital heart defects, hypospadias, orofacial clefts, and clubfoot. The risk for NTDs may be partially reduced by dietary supplementation with at least 4 mg of folic acid daily. In addition, children with maternal valproate exposure are more likely to experience cognitive developmental delay and features of autism compared with unexposed infants and infants exposed to other common antiepileptic drugs. Given that nearly half of pregnancies are unintended, clinicians who care for women of reproductive age need to consider selecting antiepileptic medications that minimize teratogenic risk while maximizing seizure control.

Treatment of **maternal depression** illustrates some of the challenges to the care of pregnant persons with maternal disease. At least 12% of pregnant persons experience depression. Maternal depression itself is associated with adverse outcomes, including obstetric complications, fetal death, preterm birth, and problems with growth. Women with depression are also more likely to have other risk factors for adverse outcomes, such as smoking, which complicates studying the impact of antidepressants on the fetus. When pharmacologic treatment of depression is required, selective serotonin reuptake inhibitors (SSRIs; including fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine) are frequently prescribed. Additionally, serotonin norepinephrine reuptake inhibitors (SNRIs; including venlafaxine and duloxetine) and tricyclic antidepressants (TCAs) have been used to treat pregnant persons with depression or anxiety disorders. Many studies have been performed to evaluate the effects of maternal antidepressant exposure during pregnancy on different adverse outcomes. Several of these have shown an increased risk of certain outcomes, including congenital malformations (in particular, congenital heart defects), preterm birth, persistent pulmonary hypertension, and respiratory distress. Some studies have attempted to compare antidepressants to determine which might produce a lower or higher risk; use of paroxetine is associated with the highest risk of birth defects among the SSRIs, and a meta-analysis suggests a lower risk for persistent pulmonary hypertension with sertraline treatment. Venlafaxine was associated with the highest number of birth defects in a case-control study of several antidepressants; however, this needs confirmation. It is difficult to differentiate the risks associated with using antidepressant medications from those of maternal depression itself or other potential confounders. In addition, although the relative risk may be increased, the outcomes for which an increased relative risk has been identified are rare; thus the absolute risk to an individual pregnancy is low. Available data on risks of antidepressant medications need to be weighed against the risks of untreated maternal depression.

Another adverse outcome that has been seen following antidepressant use during pregnancy is a condition known as **poor neonatal adaptation syndrome (PNAS)**. Poor neonatal adaptation is characterized by transient short-term adverse neonatal or neurobehavioral effects seen in the neonate. Symptoms include problems with feeding and sleeping, irritability, increased or decreased muscle tone, jitteriness, abnormal crying, gastrointestinal symptoms, and respiratory distress. Most symptoms are mild and self-limited; severe symptoms are rare. Symptoms usually develop within 48 hours after birth and last for 2-6 days. PNAS occurs in approximately 30% of infants born to mothers taking SSRIs or SNRIs; infants exposed to TCAs have a 20–50% risk of PNAS. The mechanism is not fully understood, but it is thought to be related to a withdrawal or discontinuation syndrome or possibly to serotonin toxicity. Treatment consists of supportive measures. Small, frequent, on-demand feedings; swaddling; and skin-to-skin contact are beneficial to support infants through this process. Breastfeeding may be protective in reducing PNAS and in many cases should be encouraged because many antidepressant medications are considered safe with breastfeeding. Infants can be observed on the maternity ward with their mothers unless specific symptoms warrant further evaluation and treatment. Long-term effects after PNAS have not been well studied.

Alcohol intake, typically at moderate to high levels of consumption, can result in **fetal alcohol spectrum disorder (FASD)**, a wide range of conditions resulting from exposure to alcohol during pregnancy. Fetal alcohol syndrome is on the severe end of the spectrum. Diagnostic criteria for a diagnosis of **fetal alcohol syndrome** include a confirmed history of prenatal alcohol exposure, prenatal onset of growth deficiency that persists postnatally, characteristic facial features, and neurocognitive deficits. There is no known safe level of fetal alcohol exposure; therefore pregnant persons should be counseled to abstain from alcohol consumption. **Smoking** during pregnancy is associated with an increased risk for preterm delivery, FGR, and orofacial clefts.

The use of **opioids** during pregnancy has increased substantially in the United States, which is consistent with the increased use of opioids observed in the general population. This escalation is due to an increased number of opioid prescriptions as well as increases in illicit use of heroin and fentanyl. Regular long-term use of opioids results in physiologic dependence, with withdrawal symptoms following discontinuation. An **opioid use disorder** is defined as a pattern of opioid use that includes tolerance, craving, inability to control use, and continued use despite negative consequences. Pregnant persons with an opioid use disorder should receive opioid agonist therapy along with counseling and behavioral therapy, rather than medically supervised withdrawal, because of the substantial risk for relapse with withdrawal. Studies on the use of opioids during pregnancy and the risk for congenital malformations have been inconsistent, with some showing an increased risk and others showing no increase. However, chronic use of opioids has been associated with an increased risk for other adverse pregnancy outcomes such as spontaneous abortion, PROM, preeclampsia, placental abruption, fetal death, preterm delivery, and small for gestational age.

Another complication associated with maternal opioid use during pregnancy is **neonatal opioid withdrawal syndrome (NOWS)**, also known as neonatal abstinence syndrome (NAS), a withdrawal syndrome that occurs shortly after birth in infants born to women with opioid use (including opioid treatment mediations such as methadone or buprenorphine) (see Chapter 145). Expression of NOWS can vary widely with maternal, infant, and environmental factors modifying the effects. Findings can include irritability and crying, poor state control, hypertonicity, tremors and jitteriness, failure to thrive, abnormal response to stimuli (hyper- or hyposensitivity), vomiting or diarrhea, and autonomic signs such as hiccups, tachypnea, or fever. Standardized tools are available to assess infants with NOWS. Management of the infant with NOWS includes nonpharmacologic management of the infant (e.g., comforting techniques and environmental modifications, encouraging parenting confidence), pharmacologic treatment for infants that cannot tolerate nonpharmacologic care alone, and comprehensive care of the mother. Ensuring that a safety plan for the infant is developed and that the mother is connecting to treatment resources are essential.

Certain maternal conditions are associated with an increased risk for birth defects. For example, **pregestational diabetes** (including both type 1 and type 2 diabetes present before pregnancy) is associated with a substantially increased risk for many different types of birth defects. Preconception care for women with diabetes can result in improved glucose control and a decrease in their risk for birth defects. Another common condition that increases the risk of birth defects is **maternal hyperthermia**. Fever during the first trimester of pregnancy is associated with over a twofold increased risk of NTDs and possibly other defects such as congenital heart defects, orofacial clefts, among others.

Recognition of teratogenic potential from a variety of sources offers the opportunity to prevent birth defects and other adverse outcomes. If a pregnant person is informed of the potentially harmful effects of alcohol, tobacco, and illicit drugs on her unborn infant, she may be motivated to avoid consumption of these substances during pregnancy. A woman with diabetes mellitus may significantly decrease her risk for having a child with birth defects by achieving good control of her disease before conception. When clinicians select medications for treatment of chronic conditions in adolescents, consideration should be given to medications with the least teratogenic potential, given the frequency of unintended pregnancies. Medications should only be prescribed during pregnancy after carefully weighing the maternal benefit against the potential risks of fetal harm. Medications and other agents that may affect the fetus or newborn are noted in Tables 117.6 and 117.7.

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Table 117.6 Agents Acting on Pregnant Persons That May Adversely Affect the Structure or Function of the Fetus and Newborn

Accutane (isotretinoin)	Facial-ear anomalies, heart disease, CNS anomalies
Alcohol	Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism
ACE inhibitors, angiotensin receptor antagonists	Oligohydramnios, IUGR, renal failure, Potter sequence
Azathioprine	Neonatal anemia, thrombocytopenia, and lymphopenia
Carbamazepine	Neural tube defects, possible neurodevelopmental delay
Carbimazole	Scalp defects, choanal atresia, esophageal atresia, developmental delay
Chorionic villus sampling	Possible limb reduction defects if performed before 9 weeks
Cigarette smoking	LBW for gestational age, orofacial clefts
Cocaine/crack	Placental abruption, possible vascular disruptive effects
Danazol	Virilization
Hyperthermia	Spina bifida
Lithium	Possible increased cardiac defects (Ebstein anomaly)
6-Mercaptopurine	Neonatal anemia, thrombocytopenia, lymphopenia
Methyl mercury	Minamata disease, microcephaly, deafness, blindness, intellectual disability
Methyltestosterone	Masculinization of female fetus
Misoprostol	Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus

Continued

Table 117.6 Agents Acting on Pregnant Persons That May Adversely Affect the Structure or Function of the Fetus and Newborn—cont'd

Mycophenolate mofetil	Craniofacial, limb, cardiovascular defects, spontaneous abortion
Norethindrone	Masculinization of female fetus with large doses
Penicillamine	Cutis laxa
Phenytoin	Congenital anomalies, neuroblastoma, bleeding (vitamin K deficiency)
Prednisone	Oral clefts
Stilbestrol (diethylstilbestrol [DES])	Clear cell adenocarcinoma of vagina and cervix in adolescence
Streptomycin	Deafness
Tetracycline	Pigmentation of teeth
Thalidomide	Phocomelia, deafness, other malformations
Toluene (solvent abuse)	Craniofacial abnormalities, prematurity, hypertonia
Topiramate	Cleft lip
Trimethadione and paramethadione	Spontaneous abortion, multiple malformations, cognitive impairment
Valproate	CNS (neural tube defects), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder
Warfarin (Coumadin)	Fetal bleeding and death, hypoplastic nasal structures, stippled epiphyses

ACE, Angiotensin-converting enzyme; CNS, central nervous system; IUGR, intrauterine growth restriction; LBW, low birthweight; VACTERAL, vertebral, anal, cardiac, tracheoesophageal fistula, renal, arterial, limb.

117.5 Radiation

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See also Chapter 758.

Unintentional exposure of a pregnant persons to radiation is a common cause for anxiety about whether her fetus will have genetic abnormalities or birth defects. It is unlikely that exposure to diagnostic radiation will cause gene mutations; no increase in genetic abnormalities has been identified in the offspring exposed as unborn fetuses to the atomic bomb explosions in Japan in 1945 (see Chapter 758).

A more realistic concern is whether the exposed human fetus will show birth defects or a higher incidence of malignancy. The background fetal radiation exposure in a given pregnancy is approximately 0.1 rad. The estimated radiation dose for most radiographs is <0.1 rad and for most CT scans <5 rad (maximum recommended radiation exposure in pregnancy). Imaging studies with high radiation exposure (e.g., CT scans) can be modified to ensure that radiation doses are kept as low as possible. Thus single diagnostic studies do not result in radiation doses high enough to affect the embryo or fetus. Pregnancy termination should not be recommended only on the basis of diagnostic radiation exposure. Most of the evidence suggests that usual fetal radiation exposure does not increase the risk of childhood leukemia and other cancers; although some sources suggest that a 1-2 rad fetal radiation exposure may confer a 1.5–2-fold increased risk of childhood leukemia, which has a background risk of 1 in 3,000. Before implantation (0-2 weeks' postconception), radiation doses of 5-10 rad may result in miscarriage. At 2-8 weeks' gestation, doses in excess of 20 rad have been associated with congenital anomalies and FGR. Severe intellectual disabilities can occur with exposures of ≥25 rad before 25 weeks' gestation. The available data suggest no harmful fetal effect of diagnostic MRI or US, which do not involve radiation.

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117.6 Intrauterine Diagnosis of Fetal Disease

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See Table 117.1 and Chapter 117.2.

Diagnostic procedures are used to identify fetal diseases when direct fetal treatment is possible to better direct neonatal care, when a decision is made to deliver a viable but premature infant to avoid IUFD, or when pregnancy termination is being considered. Fetal assessment is also indicated in a broader context when the family, medical, or reproductive history of the mother suggests the presence of a high-risk pregnancy or a high-risk fetus (see Chapters 116 and 117.3).

Various methods are used for identifying fetal disease (see Table 117.1). Fetal US imaging may detect fetal growth abnormalities (by previously outlined biometric measurements) or fetal malformations (Fig. 117.7). Serial determinations of growth velocity and the head-to-abdomen circumference ratio enhance the ability to detect IUGR. Real-time US may identify placental abnormalities (abruptio placentae, placenta previa) and fetal anomalies such as hydrocephalus, NTDs, duodenal atresia, diaphragmatic hernia, renal agenesis, bladder outlet obstruction, congenital heart disease, limb abnormalities, sacrococcygeal teratoma, cystic hygroma, omphalocele, gastroschisis, and hydrops (Table 117.8).

Real-time US also facilitates performance of needle-guided procedures (i.e., cordocentesis) and the BPP by imaging can assess fetal breathing, body movements, tone, and amniotic fluid volume (see Table 117.2). Doppler velocimetry assesses fetal arterial blood flow (vascular resistance) (see Figs. 117.4 and 117.5). Fetal MRI is used to better define abnormalities detected on US and to help with prognostication (see Fig. 117.1).

Table 117.7 Agents Acting on Pregnant Persons That May Adversely Affect the Newborn Infant

Acebutolol—IUGR, hypotension, bradycardia
Acetazolamide— transient metabolic acidosis
Amiodarone—bradycardia, neonatal thyroid dysfunction
Aspirin (high dose)—neonatal bleeding, premature closure of ductus arteriosus, renal failure
Atenolol—IUGR, bradycardia
Baclofen—withdrawal
Blue cohosh herbal tea—neonatal heart failure
Bromides—CNS depression
Captopril, enalapril—anuric renal failure, oligohydramnios
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor—CNS depression, hypotonia
Fluoxetine and other SSRIs—difficulties with neonatal adaptation, slight increased risk of persistent pulmonary hypertension
Haloperidol—withdrawal, transient neonatal tardive dyskinesia
Ibuprofen—premature closures of ductus arteriosus, renal failure
Imipramine—withdrawal, transient hypotonia
Indomethacin—premature closure of ductus arteriosus, renal failure
Iodide (radioactive)—goiter
Iodides—goiter
Lead—reduced intellectual function
Magnesium sulfate—respiratory depression, hypotonia
Methimazole—goiter, hypothyroidism
Morphine and its derivatives (addiction)—withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Nitrofurantoin—hemolytic anemia
Oxytocin—hyperbilirubinemia, hyponatremia
Phenobarbital—bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine—hemolytic anemia (in G6PD-deficient infants)
Propranolol—hypoglycemia, bradycardia, apnea
Propylthiouracil—goiter, hypothyroidism
Reserpine—transient neonatal respiratory distress
Sulfonamides—hyperbilirubinemia, kernicterus
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia, possible increased risk of infection during first year of life
Valproate—developmental delay, attention-deficit/hyperactivity disorder
Zolpidem (Ambien)—low birthweight, preterm delivery

CNS, Central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.
See also Table 117.6.

Amniocentesis, the transabdominal withdrawal of amniotic fluid during pregnancy for diagnostic purposes (see Table 117.1), is a common obstetric procedure. It is frequently performed to evaluate for infection. It is also done for genetic indications, usually between the 15th and 20th weeks of gestation, with results available as soon as 24-48 hours for fluorescence in situ hybridization (FISH) testing and 2-3 weeks for microarray testing. The most common indication for genetic amniocentesis is **advanced maternal age**; the risk for chromosome abnormality at term at age 21 years is 1:525, vs 1:6 at age 49 years. ACOG recommends that all pregnant persons be offered amniocentesis to evaluate further for an underlying genetic condition such as Down syndrome. Analysis of amniotic fluid may also help in identifying NTDs (elevation of α-fetoprotein [AFP] and presence of acetylcholinesterase). Additionally, families with a known genetic syndrome may be offered prenatal genetic testing from amniotic fluid or amniocytes obtained via amniocentesis or **chorionic villus sampling (CVS).**

Chorionic villus sampling (CVS) is performed in the first trimester, either transvaginally or transabdominally. The sample obtained is placental in origin, which can sometimes be problematic because aneuploidy may be present in the placenta and not the fetus, a condition known as **confined placental mosaicism**, which can give a false-positive rate as high as 3%. Furthermore, CVS may be associated with a slightly higher risk of fetal loss than amniocentesis.

Amniocentesis can be carried out with little discomfort to the mother. Procedure-related complications are relatively rare, and many can be avoided by using a US-guided approach. These risks include direct damage to the fetus, placental puncture and bleeding with secondary damage to the fetus, stimulation of uterine contraction and premature labor, chorioamnionitis, maternal sensitization to fetal blood, and pregnancy loss. Best available data indicate that the pregnancy loss rate associated with amniocentesis is 1:500-900 procedures. Amniocentesis is not recommended before 14 weeks of gestation because this has been associated with a higher risk of pregnancy loss, ruptured membranes, and clubfoot.

Cordocentesis, or percutaneous umbilical blood sampling (PUBS), is used to diagnose and treat fetal hematologic abnormalities, genetic disorders, infections, and fetal acidosis (see Table 117.1). Under direct US visualization, a long needle is passed into the umbilical vein at its entrance to the placenta or in a free loop of cord. Transfusion or administration of drugs can be performed through the umbilical vein (Table 117.9). The predominant indication for this procedure is for confirmation of fetal anemia (in Rh isoimmunization) or thrombocytopenia (NAIT), with subsequent transfusion of packed red blood cells or platelets into the umbilical venous circulation. The risk of fetal fatality with PUBS procedure is 1%, but can be higher with certain fetal conditions, such as nonimmune hydrops.

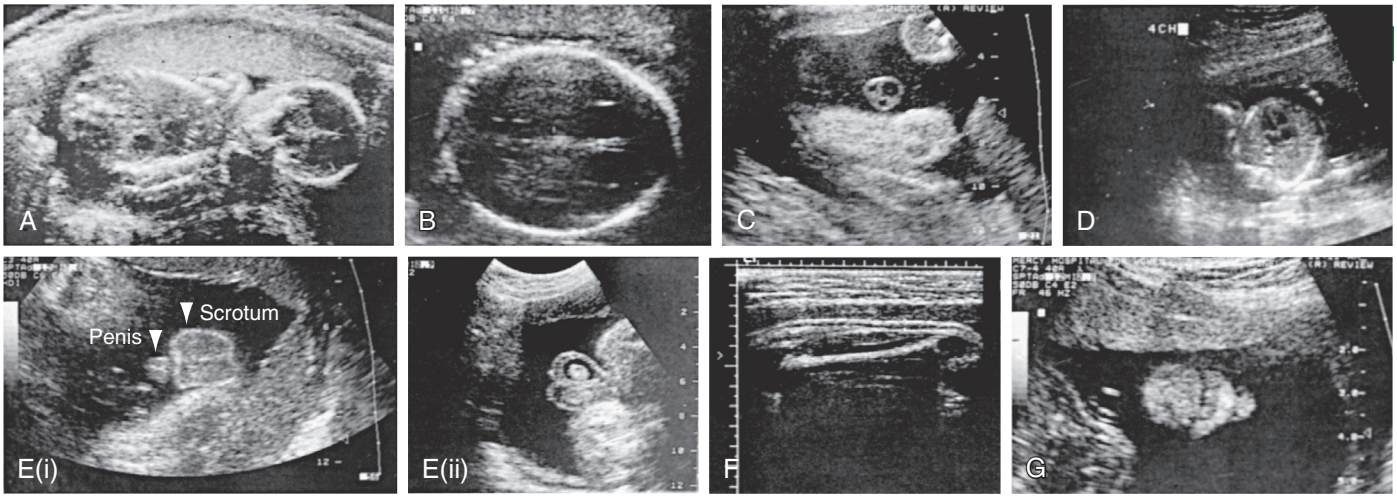

Fig. 117.7 Assessment of fetal anatomy. **A,** Overall view of the uterus at 24 weeks showing a longitudinal section of the fetus and an anterior placenta. **B,** Transverse section at the level of the lateral ventricle at 18 weeks showing (on the right) prominent anterior horns of the lateral ventricles on either side of the midline echo of the falx. **C,** Cross section of the umbilical cord showing that the lumen of the umbilical vein is much wider than that of the two umbilical arteries. **D,** Four-chambered view of the heart at 18 weeks with equal-sized atria. **E(i),** Normal male genitals near term. **E(ii),** Hydrocele outlining a testicle within the scrotum projecting into a normal-sized pocket of amniotic fluid at 38 weeks. Approximately 2% of male infants after birth have clinical evidence of a hydrocele that is often bilateral, not to be confused with subcutaneous edema occurring during vaginal breech birth. **F,** Section of a thigh near term showing thick subcutaneous tissue (4.6 mm between *markers*) above the femur of a fetus with macrosomia. **G,** Fetal face viewed from below, showing (from right to left) the nose, alveolar margin, and chin at 20 weeks. (*From Special investigative procedures. In Beischer NA, Mackay EV, Colditz PB, eds., Obstetrics and the Newborn. 3rd ed. Philadelphia: Saunders; 1997.*)

Table 117.8 Significance of Fetal Ultrasonographic Anatomic Findings

PRENATAL OBSERVATION	DEFINITION	DIFFERENTIAL DIAGNOSIS	SIGNIFICANCE	POSTNATAL EVALUATION
Dilated cerebral ventricles	Ventriculomegaly ≥10 mm	• Hydrocephalus • Hydranencephaly • Dandy-Walker cyst • Agenesis of corpus callosum • Volume loss	• Transient isolated ventriculomegaly is common and usually benign • Persistent or progressive ventriculomegaly is more worrisome • Identify associated cranial and extracranial anomalies	• Serial head US or MRI • Evaluate for extracranial anomalies
Choroid plexus cysts	Size ~10 mm: unilateral or bilateral 1–3% incidence	• Abnormal karyotype (trisomy 18, 21) • Increased risk if AMA	• Often isolated, benign; resolves by 24-28 wk • Fetus should be examined for other organ anomalies; if additional anomalies present, amniocentesis should be performed for karyotype	• Head US • Examine for extracranial anomalies • Karyotype if indicated
Nuchal fold thickening	≥6 mm at 15-20 wk	• Cystic hygroma, trisomy 21, 18 • Turner syndrome (XO) • Other genetic syndromes • Normal (~25%)	• ~50% of affected fetuses have chromosome abnormalities • Amniocentesis for karyotype needed	• Examine for multiple organ malformation • Karyotype if indicated
Dilated renal pelvis	Pyelectasis ≥4 to 10 mm 0.6–1% incidence	• Normal variant • Uteropelvic junction obstruction • Vesicoureteral reflux • Posterior ureteral valves • Ectopic ureterocele • Large-volume nonobstruction	• Often "physiologic" and transient • Reflux is common • If dilation is >10 mm or associated with caliectasis, pathologic cause should be considered • If large bladder present, posterior urethral valves and megacystis–microcolon hypoperistalsis syndrome should be considered	• Repeat ultrasonography on day 5 and at 1 mo • Voiding cystourethrogram • Prophylactic antibiotics
Echogenic bowel	0.6% incidence	• CF, meconium peritonitis • Trisomy 21 or 18, other chromosomal abnormalities • Cytomegalovirus, toxoplasmosis, GI obstruction • Intrauterine bleeding (fetal swallowing of blood)	• Often normal • Consider CF, aneuploidy, and TORCH	• Sweat chloride and DNA testing • Karyotype • Surgery for obstruction • Evaluation for TORCH
Stomach appearance	Small or absent or with double bubble	• Upper GI obstruction (esophageal atresia) • Double bubble signifies duodenal atresia • Aneuploidy • Polyhydramnios • Stomach in chest signifies diaphragmatic hernia	• Must also consider neurologic disorders that reduce swallowing • >30% with double bubble have trisomy 21	• Chromosomes • Kidney, ureter, and bladder radiograph if indicated • Upper GI series • Neurologic evaluation

AMA, Advanced maternal a… …; CF, cystic fibrosis; GI, gastrointestinal; TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex syndrome; US, ultrasound.

Table 117.9 Fetal Therapy

DISORDER	POSSIBLE TREATMENT
HEMATOLOGIC	
Anemia with hydrops (erythroblastosis fetalis)	Cordocentesis of umbilical vein with packed red blood cell transfusion
Isoimmune thrombocytopenia	Umbilical vein platelet transfusion, maternal IVIG
Autoimmune thrombocytopenia (ITP)	Maternal steroids and IVIG
METABOLIC/ENDOCRINE	
Maternal PKU	Phenylalanine restriction
Fetal galactosemia	Galactose-free diet (?)
Multiple carboxylase deficiency	Biotin if responsive
Methylmalonic acidemia	Vitamin B_{12} if responsive
21-Hydroxylase deficiency	Dexamethasone if female fetus
Maternal diabetes mellitus	Tight insulin control during pregnancy, labor, and delivery
Fetal goiter	Maternal hyperthyroidism—maternal propylthiouracil Fetal hypothyroidism—intraamniotic thyroxine
Bartter syndrome	Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses
FETAL DISTRESS	
Hypoxia	Maternal oxygen, position changes
Intrauterine growth restriction	Improve macronutrients and micronutrients if deficient, smoking cessation, treatment of maternal disease, antenatal fetal surveillance
Oligohydramnios, premature rupture of membranes with variable deceleration	Antenatal fetal surveillance Approach dependent on etiology Amnioinfusion (intrapartum)
Polyhydramnios	Antenatal fetal surveillance Approach dependent on etiology Amnioreduction if indicated,
Supraventricular tachycardia	Maternal digoxin,* flecainide, procainamide, amiodarone, quinidine
Lupus anticoagulant	Maternal aspirin and heparin
Meconium-stained fluid	Amnioinfusion
Congenital heart block	Dexamethasone, pacemaker (with hydrops)
Premature labor	Magnesium sulfate, nifedipine, indomethacin with antenatal corticosteroids (betamethasone)
RESPIRATORY	
Pulmonary immaturity	Betamethasone
Bilateral chylothorax—pleural effusions	Thoracentesis, pleuroamniotic shunt
Severe diaphragmatic hernia	Fetoscopic tracheal occlusion
CONGENITAL ABNORMALITIES†	
Neural tube defects	Folate, vitamins (prevention); fetal surgery‡
Posterior urethral valves, urethral atresia (lower urinary tract obstruction)	Percutaneous vesicoamniotic shunt
Cystic adenomatoid malformation (with hydrops)	Pleuroamniotic shunt or resection‡
Fetal neck masses	Secure an airway with EXIT procedure‡
INFECTIOUS DISEASE	
Group B *Streptococcus* colonization	Ampicillin, penicillin
Chorioamnionitis	Antibiotics and delivery
Toxoplasmosis	Spiramycin, pyrimethamine, sulfadiazine, folic acid
Syphilis	Penicillin
Tuberculosis	Antituberculosis drugs
Lyme disease	Penicillin, ceftriaxone
Parvovirus	Intrauterine red blood cell transfusion for hydrops, severe anemia
Chlamydia trachomatis	Azithromycin
HIV-AIDS	Maternal and neonatal antiretroviral therapy (see Chapter 322)
Cytomegalovirus	No approved prenatal treatments
OTHER	
Nonimmune hydrops (anemia)	Umbilical vein packed red blood cell transfusion
Narcotic abstinence (withdrawal)	Maternal methadone maintenance
Sacrococcygeal teratoma (with hydrops)	In utero resection or catheter-directed vessel obliteration
Cardiac rhabdomyoma	Maternal sirolimus
Intrapericardial teratoma	Fetal surgery
CRISPR-*Cas9* gene editing	Proof of concept in previable in vitro fertilized human embryos
Twin-twin transfusion syndrome	Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photocoagulation of shared vessels
Twin reversed arterial perfusion (TRAP) syndrome	Cord occlusion, radiofrequency ablation
Multifetal gestation	Selective reduction
Neonatal hemochromatosis	Maternal IVIG
Aortic stenosis	In utero valvuloplasty

*Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.
†Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.
‡EXIT permits surgery and other procedures.
EXIT, Ex utero intrapartum treatment; IVIG, intravenous immunoglobulin; PKU, phenylketonuria; (?), possible but not proved efficacy.

Aneuploidy screening is offered to pregnant persons in the first trimester or at midgestation to evaluate the risk for common aneuploidies such as Down syndrome (trisomy 21), trisomy 18, trisomy 13, and congenital malformations (e.g., abdominal wall or NTDs) known to cause elevations of various markers. A combination of these biochemical markers (including AFP, inhibin A, estriol, pregnancy-associated plasma protein A, β-human chorionic gonadotropin [β-hCG]) and US increases the positive predictive value (PPV) of these screening tests. Fetal DNA in maternal plasma and fetal cells circulating in maternal blood are potential noninvasive sources of material for prenatal genetic testing. This testing, however, is not diagnostic, and a positive test requires either amniocentesis or postnatal analysis to confirm the diagnosis. Nonetheless, fetal karyotyping by analysis of fetal DNA in maternal plasma is another screening test that is very sensitive for the detection of Down syndrome, with a higher PPV than any other prenatal screening test for Down syndrome. Currently, however, the use of this technology is only advocated in pregnancies deemed at high risk for aneuploidy.

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117.7 Treatment and Prevention of Fetal Disease

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See also Chapter 118.

Management of a fetal disease depends on coordinated advances in diagnostic accuracy and knowledge of the disease's natural history; an understanding of fetal nutrition, pharmacology, immunology, and pathophysiology; the availability of specific active drugs that cross the placenta; and therapeutic procedures. Progress in providing specific treatments for accurately diagnosed diseases has improved with the advent of real-time ultrasonography, amniocentesis, and cordocentesis (see Tables 117.1 and 117.9).

The incidence of sensitization of Rh-negative women by Rh-positive fetuses has been reduced by prophylactic administration of Rh(D) immunoglobulin to mothers early in pregnancy and after each delivery or abortion, thus reducing the frequency of hemolytic disease in their subsequent offspring. **Fetal erythroblastosis** (see Chapter 140) may be accurately detected by fetal Doppler assessment of the peak systolic velocity of the middle cerebral artery and treated with intrauterine transfusions of packed Rh-negative blood cells via the intraperitoneal or, more often, intraumbilical vein approach.

Pharmacologic approaches to fetal immaturity mostly revolve around the administration of antenatal corticosteroids to the mother to promote fetal production of surfactant with a resultant decrease in the incidence of **respiratory distress syndrome** (see Chapter 126). Tocolytic agents have been demonstrated to prolong pregnancy to allow the administration of antenatal corticosteroids (48 hours); however, there is no proven benefit beyond this time frame. Maternal administration of magnesium sulfate for fetal/neonatal neuroprotection is recommended in pregnancies deemed to be at risk of imminent delivery before 32 weeks' gestation in light of evidence demonstrating a reduction in frequency of cerebral palsy compared with those who did not receive this treatment.

Management of definitively diagnosed fetal genetic disease or congenital anomalies consists of multidisciplinary parental counseling. Rarely, high-dose **vitamin therapy** for a responsive inborn error of metabolism (e.g., biotin-dependent disorders) or fetal transfusion (with red blood cells or platelets) may be indicated. **Fetal surgery** is well-established treatment for certain conditions but remains a largely experimental approach to therapy for other conditions and is available only in a few, highly specialized perinatal centers (see Table 117.9 and Chapter 118). The nature of the defect and its consequences must be considered, as well as ethical implications for the fetus and the parents. **Termination of pregnancy** is also an option that should be discussed during the initial phases of counseling.

Folic acid supplementation decreases the incidence and recurrence of NTDs. Because the neural tube closes within the first 28 days of conception, periconceptional supplementation is needed for prevention. It is recommended that women without a prior history of a NTD ingest 400 μg/day of folic acid throughout their reproductive years. Women with a history of a prior pregnancy complicated by an NTD or a first-degree relative with an NTD should have preconceptional counseling and should ingest 4 mg/day of supplemental folic acid beginning at least 1 month before conception. Fortification of cereal-grain flour with folic acid is established policy in the United States and some other countries. The optimal concentration of folic acid in enriched grains is somewhat controversial. The incidence of NTD in the United States and other countries has decreased significantly since these public health initiatives were implemented. Use of some antiepileptic drugs (valproate, carbamazepine) during pregnancy is associated with an increased risk of NTD. Women taking these medications should ingest 1-5 mg of folic acid daily in the preconception period.

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Chapter 118

Fetal Intervention and Surgery

Natalie E. Rintoul, Emily A. Partridge, and Holly L. Hedrick

Congenital anomalies have always been recognized as a therapeutic challenge. Numerous diagnoses have been evaluated for the possibility of fetal intervention (Tables 118.1 and 118.2). Some have proved beneficial to the developing infant, some have been abandoned, and some remain under investigation.

FETAL THERAPY ETHICS

With the development of advanced fetal ultrasound (US), ultrafast fetal MRI, and fetal echocardiography, the ability to accurately diagnose fetal disease has improved substantially over the past 3 decades. The first prenatal therapeutic intervention was reported in 1963 with the successful treatment of erythroblastosis fetalis by fetal intraperitoneal infusion. Other innovations, though groundbreaking, brought to light the high morbidity (fetal and maternal) and mortality associated with open fetal interventions, and it would take greater experience and techniques before open fetal surgery would be safer and therapeutic.

OBSTRUCTIVE UROPATHY

Obstructive uropathy is a diverse set of diseases affecting the bladder neck or urethra and affects between 2.2 and 3.3 per 10,000 live births. It is most frequently caused by **posterior urethral valves (PUVs)** but can be caused by a variety of other defects, including urethral atresia, persistent cloaca, caudal regression, and megacystis–microcolon–intestinal hypoperistalsis syndrome (see Chapters 577 and 578). Although male fetuses are more commonly affected, females are more commonly associated with severe pathologic variants, and 30% of survivors will require renal replacement therapy or transplantation before age 5. Congenital obstructive uropathy

Table 118.1 Fetal Diagnoses Evaluated and Treated in Fetal Centers

Amniotic band syndrome (ABS)	Gastroschisis
Anomalies in monochorionic twins	Hydrocephalus
Aortic stenosis	Hydronephrosis
Arachnoid cyst	Hypoplastic left heart syndrome (HLHS)
Bladder exstrophy	Imperforate anus
Bladder outlet obstruction	Intraabdominal cyst
Bronchopulmonary sequestration (BPS)	Lymphangioma
Cervical teratoma	Mediastinal teratoma
Cloaca	Myelomeningocele, spina bifida
Cloaca exstrophy	Neuroblastoma
Complete heart block	Obstructive uropathy
Congenital pulmonary airway malformation (CPAM)	Omphalocele
Congenital diaphragmatic hernia (CDH)	Pentalogy of Cantrell
Congenital high airway obstruction syndrome (CHAOS)	Pericardial teratoma
EXIT to airway procedure for CHAOS	Pleural effusions
Conjoined twins	Pulmonary agenesis
Dandy-Walker malformation	Pulmonary atresia with intact ventricular septum
Duodenal atresia	Sacrococcygeal teratoma (SCT)
Encephalocele	Twin reversed arterial perfusion (TRAP) sequence
Enteric duplication atresia	Twin-to-twin transfusion syndrome (TTTS)
Esophageal atresia	Vein of Galen aneurysm

EXIT, Ex utero intrapartum treatment.

Table 118.2 Indications and Rationales for In Utero Surgery on the Fetus, Placenta, Cord, or Membranes

FETAL SURGERY	PATHOPHYSIOLOGY	RATIONALE FOR IN UTERO INTERVENTION
SURGERY ON THE FETUS		
1. Congenital diaphragmatic hernia	Pulmonary hypoplasia and anatomic substrate for pulmonary hypertension	Reversal of pulmonary hypoplasia and reduced degree of pulmonary hypertension Repair of actual defect delayed until after birth
2. Lower urinary tract obstruction	Progressive renal damage due to obstructive uropathy Pulmonary hypoplasia due to oligohydramnios	Prevention of renal failure and pulmonary hypoplasia by anatomic correction or urinary deviation
3. Sacrococcygeal teratoma	High-output cardiac failure due to AV shunting and/or bleeding Direct anatomic effects of the tumoral mass Polyhydramnios-related preterm labor	Reduction of functional impact of tumor by ablation of tumor or (part of) its vasculature Reduction of anatomic effects by drainage of cysts or bladder Amnioreduction preventing obstetric complications
4. Thoracic space-occupying lesions	Pulmonary hypoplasia (space-occupying mass) Hydrops due to impaired venous return (mediastinal compression)	Creation of space for lung development Reversal of the process of cardiac failure
5. Neural tube defects	Damage to exposed neural tube Chronic CSF leak, leading to Arnold-Chiari malformation and hydrocephalus	Prevention of exposure of the spinal cord to amniotic fluid Restoration of CSF pressure correcting Arnold-Chiari malformation
6. Cardiac malformations	Critical lesions causing irreversible hypoplasia or damage to developing heart	Reversal of process by anatomic correction of restrictive pathology
SURGERY ON THE PLACENTA, CORD, OR MEMBRANES		
7. Chorioangioma	High-output cardiac failure due to AV shunting Effects of polyhydramnios	Reversal of process of cardiac failure and hydrops fetoplacentalis by ablation or reduction of flow
8. Amniotic bands	Progressive constrictions causing irreversible neurologic or vascular damage	Prevention of amniotic band syndrome leading to deformities and function loss
9. Abnormal monochorionic twinning: twin-to-twin transfusion; fetus acardius, and discordant anomalies	Twin-twin transfusion leading to oligopolyhydramnios sequence, hemodynamic changes; preterm labor, and rupture of membranes; in utero damage to brain, heart, or other organs In utero fetal death may cause damage to co-twin Cardiac failure of pump twin and consequences of polyhydramnios Serious anomaly raising the question of termination of pregnancy Selective feticide	Arrest of intertwin transfusion Prevention/reversal of cardiac failure and/or neurologic damage, including at in utero death Prolongation of gestation Selective feticide to arrest parasitic relationship, to prevent consequences of in utero fetal death, and to avoid termination of entire pregnancy

AV, Arteriovenous; CSF, cerebrospinal fluid.
From Deprest J, Hodges R, Gratacos E, Lewi L. Invasive fetal therapy. In: Creasy RK, Resnik R, Iams JD, et al., eds. *Creasy & Resnik's Maternal-Fetal Medicine*. 7th ed. Philadelphia: Elsevier; 2014. Table 35-1.

causes hydronephrosis and renal dysplasia of variable severity. Although the mechanism of renal injury is debated, hypotheses include cyst formation secondary to urinary retention and subsequent disruption of nephrogenesis versus obstruction-associated apoptosis of renal tubular cells.

Obstructive uropathy usually presents on fetal US with an enlarged bladder, bilateral hydroureteronephrosis, and oligohydramnios in the second and third trimester. Mild forms of obstructive uropathy may lead to minimal short- or long-term clinical sequelae. However, reduced fetal urine output resulting in oligohydramnios or anhydramnios in more severe forms can cause significant pulmonary hypoplasia, which is associated with death shortly after delivery in >80% of infants. Pulmonary survivors remain subject to high mortality and chronic morbidity resulting from renal dysplasia, renal failure, and the need for chronic renal replacement therapy. Workup of congenital obstructive uropathy includes genetic and structural evaluation, with additional imaging and fetal urinalysis aiding in prognostication. For example, a fetal urine sodium <100 mEq/L, chloride <90 mEq/L, and urine osmolality >210 mEq/L at a mean gestational age of 23.8 weeks predicts "good outcome," as reflected by the presence of nondysplastic kidneys at autopsy or biopsy, or normal renal and pulmonary function at birth. Fetuses with salvageable renal function should have downtrending values of urine sodium, chloride, calcium, total protein and β_2-microglobulin on repeat vesicocentesis. Fetal bladder filling time [(fetal bladder volume 48 hours post-vesicocentesis – fetal bladder volume prior to vesicocentesis)/fetal bladder volume prior to vesicocentesis)], fetal MRI, and three-dimensional fetal cystoscopy have also been shown to have utility in predicting postnatal renal function.

The primary objective of fetal intervention in fetuses with obstructive uropathy is restoration of amniotic fluid volume to prevent pulmonary hypoplasia. Although prevention of ongoing renal injury is also desired, the efficacy of fetal intervention in achieving this goal is uncertain. Therefore fetal intervention for obstructive uropathy is currently limited to fetuses in whom the obstruction is sufficient to cause oligohydramnios or anhydramnios.

For fetuses that still have adequate renal function and can produce urine, treatment options include vesicoamniotic shunting, valve ablation via cystoscopy, and vesicostomy. **Vesicoamniotic shunting** is the most common and involves percutaneous, US-guided placement of a double-pigtailed shunt from the fetal bladder to the amniotic space, allowing decompression of the obstructed bladder and restoration of the amniotic fluid volume (Figs. 118.1 and 118.2). Although simple in concept, bladder decompression may not always occur, and many catheters will become dislodged as the fetus develops; a fetus typically requires three catheter replacements before completion of pregnancy. Vesicoamniotic shunting may improve perinatal survival, but at the expense of poor long-term renal function. In a systematic review of over 250 fetuses, increased prenatal survival is present in the shunted population, but there is no difference in the 12- and 24-month survival.

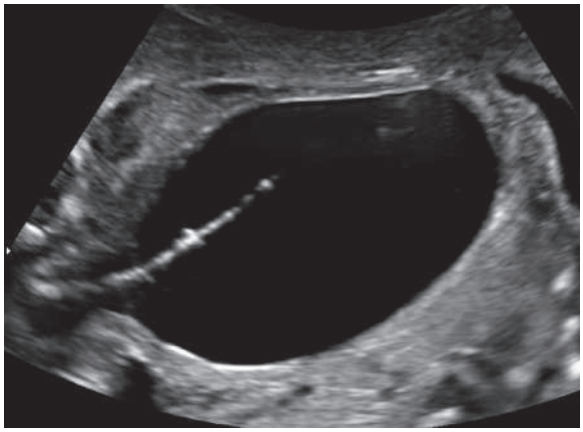

Fig. 118.1 Ultrasound image showing fetoscopic placement of a transurethral vesicoamniotic shunt in a patient with posterior urethral valves. *(Courtesy Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)*

Fetal **cystoscopy** is more technically challenging than vesicoamniotic shunt placement, more invasive, and requires more sedation, but this option holds some important advantages. Cystoscopy allows for direct visualization of the obstruction and does not require amnioinfusion. Moreover, when the obstruction is visualized and the diagnosis of PUV confirmed, the valves can be treated, restoring urine flow to the amniotic space, and eliminating the need for repeated fetal interventions in most patients. Creation of a vesicostomy (direct opening from bladder through fetal abdominal wall) by open fetal surgery has improved perinatal survival (Fig. 118.3). However, the current dataset evaluating this approach is still limited, and direct comparisons to shunting suggest no significant difference between these interventions.

NONOBSTRUCTIVE RENAL DISEASE

Nonobstructive fetal renal disease can result from renal hypoplasia/dysplasia and from genetic diseases such as autosomal recessive polycystic kidney disease. Similar to obstructive uropathy, fetal therapy is focused on restoring amniotic fluid volume in patients with oligohydramnios or anhydramnios. However, restoration of amniotic fluid volume in nonobstructive renal disease requires external sources of amniotic fluid. Current treatment options include serial percutaneous **amnioinfusion** and infusion of fluid by amnioport. Serial amnioinfusions are less invasive as a single procedure, but most pregnancies will require weekly infusions to maintain adequate amniotic fluid volume. Amnioinfusion through an amnioport involves open surgical placement of a catheter into the amniotic space that is connected to an ex utero subcutaneous port. This allows repeated fluid infusion into the amniotic space. The amnioport is more challenging and invasive as an individual procedure but provides more reliable access to the amniotic space for the duration of the pregnancy. Small studies suggest both these procedures improve pulmonary outcomes and perinatal survival in infants with renal disease, but these infants will require dialysis and then renal transplant when the infant is large enough (2-3 years of age). The Renal Anhydramnios Fetal Therapy (RAFT) is a multi-site clinical trial to determine the feasibility, safety and success rate of serial **amnioinfusions** for early pregnancy renal anhydramnios (EPRA). The trial originally included EPRA caused both by congenital bilateral **renal agenesis** (CoBRA) and by fetal renal failure

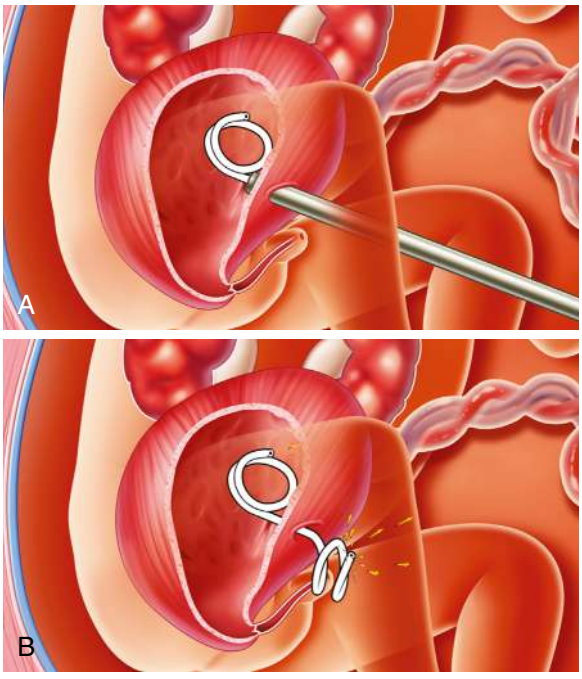

Fig. 118.2 Vesicoamniotic shunt placement. **A**, The shunt is loaded into the trocar, passed into the bladder, and recoils to a pigtail shape. **B**, The other end of the shunt recoils to a pigtail outside the abdominal wall, releasing urine into the amniotic fluid space around the fetus. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

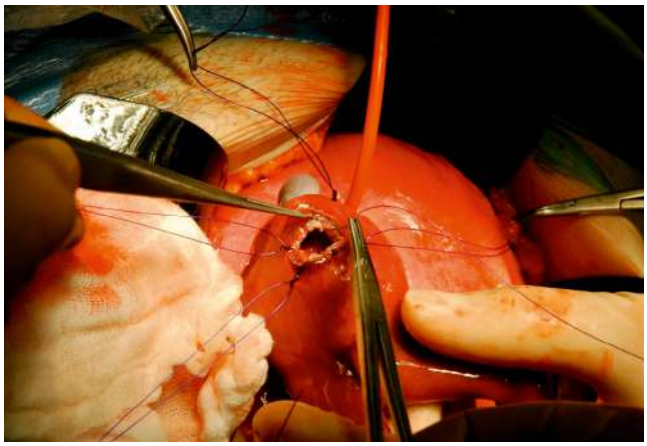

Fig. 118.3 Creation of a fetal vesicostomy. The uterine opening is stapled to prevent bleeding, and a catheter is inserted to replace amniotic fluid and maintain uterine volume. The fetus is positioned with the legs to the lower part of the field and the umbilical cord to the upper part of the field. A vesicostomy is created through the bladder and the abdominal wall to allow drainage of the obstructed bladder and restoration of amniotic fluid volume. *(Courtesy Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)*

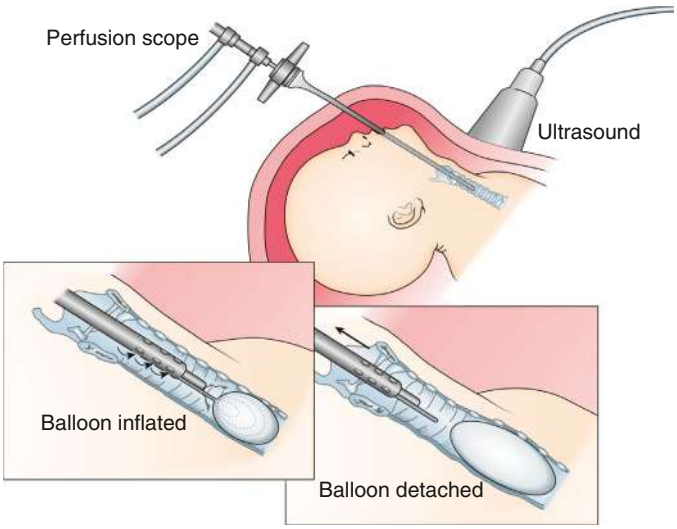

Fig. 118.4 Technique for fetoscopic tracheal occlusion using a balloon. *(Modified from Hirose S, Harrison MR. Fetal therapy. In Holcomb GW III, Murphy JP, eds. Ashcraft's Pediatric Surgery. 5th ed. St Louis: Elsevier; 2010. Fig. 10.1.)*

(FRF) with kidney tissue present. At the time of this publication, the CoBRA arm is no longer recruiting. The primary objective of this trial is to determine the proportion of neonates surviving to successful dialysis after serial amnioinfusions.

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is a structural birth defect in which the diaphragm fails to fully close during development resulting in herniation of the abdominal contents into the thorax and inhibition of fetal lung growth (see Chapter 131). CDH occurs in 1,500 live births in the United States annually and is the leading cause of in-hospital neonatal deaths as well as the costliest noncardiac birth defect. Although the pathophysiology of CDH remains unclear, most patients are affected by some degree of pulmonary hypoplasia and persistent pulmonary hypertension. A dual-hit hypothesis has been suggested to characterize lung injury in CDH, with an initial injury occurring during organogenesis resulting in bilateral pulmonary hypoplasia and a secondary insult of the ipsilateral lung due to compression by the herniated abdominal viscera. Fetal breathing and fluidic lung distension are features of normal lung development, which are mechanically compromised by the diaphragmatic defect, resulting in not only reduced parenchymal volume but also decreased vascular density. Compensatory vascular remodeling results in hypermuscularization of the arteriolar bed, increased vascular resistance, and ultimately pulmonary hypertension. It is the severity of pulmonary hypoplasia and persistent pulmonary hypertension that represents the greatest determinant of morbidity and mortality.

In mild cases of CDH, surgical repair of the diaphragm is typically performed in the first few days of life after respiratory and hemodynamic stabilization. Although these infants are affected by pulmonary hypoplasia and close monitoring is required during the first years of life, long-term outcomes are excellent in the majority of survivors of mild CDH. In cases of *severe* CDH, pulmonary hypertension leads to right ventricular dysfunction and right-to-left shunting across the patent foramen ovale and ductus arteriosus, which can result in left ventricular dysfunction and cardiac failure necessitating extracorporeal membrane oxygenation (ECMO) in the perinatal period. Mortality is high in severely affected infants, and survivors often have significant impairments in long-term respiratory, feeding, and neurodevelopmental outcomes.

More than half of all CDH cases are identified on routine second trimester anatomy US, whereas delayed diagnosis may occur secondary to small defects, technical limitations, or unavailability of prenatal care. In 50–70% of cases the lesion is isolated, whereas *syndromic* or *complex* CDH may be associated with additional anomalies warranting further imaging and genetic studies. Fetal echocardiography and ultrafast MRI should be included in comprehensive fetal diagnosis, permitting calculation of fetal lung volumes as well as ruling out major structural cardiac anomalies.

The first reports of attempted *in utero repair* of CDH noted impairment of umbilical blood flow after reduction of the liver resulting in fetal demise in a number of cases. Although the procedure proved to be technically feasible in fetuses without liver herniation, comparative analysis revealed higher rates of preterm delivery (32 vs 38 weeks' gestation) and similar rates of survival (75% fetal repair vs 86% postnatal repair), leading to abandonment of prenatal attempts at surgical repair.

Given the disappointing results after attempted open fetal surgical repair of **CDH**, researchers turned to the fetal lamb model to assess the impact of tracheal ligation on pulmonary development. By blocking the efflux of fetal lung fluid into the amniotic space, pulmonary distension results in increased lung volumes. To mitigate the risks associated with open tracheal ligation, a **fetoscopic endoluminal tracheal occlusion (FETO)** approach with balloon tracheal occlusion was developed (Fig. 118.4). In a study of 210 fetuses with *severe* hypoplasia due to isolated CDH, the use of FETO had an acceptable safety profile in the mother with improved neonatal survival but increased risk of preterm birth. In this trial the balloon was inserted at approximately 28 weeks of gestation and removal at 34 weeks, with this timing based on the hypothesis that tracheal occlusion will promote lung expansion while removal of the balloon before delivery will promote alveolar type II cell maturation. The multicenter prospective randomized Tracheal Occlusion to Accelerate Lung Growth (TOTAL) study results had inclusion criteria of gestational age less than 29 weeks 6 days at randomization, isolated left-sided CDH with no other major structural or chromosomal defects, and severe pulmonary hypoplasia defined as observed-to-expected lung-to-head ratios of less than 25%. Forty percent of infants with severe CDH in the FETO group survived to discharge compared to 15% in the expectant care group, with survival to 6 months identical to survival at discharge and increased rate of preterm rupture of membranes (47% vs 11%) and preterm birth (75% vs 29%).

CONGENITAL PULMONARY AIRWAY MALFORMATION

Congenital pulmonary airway malformations (CPAM), or fetal lung lesions, are a group of rare congenital pulmonary neoplasms including congenital cystic adenomatoid malformations (CCAMs), bronchopulmonary sequestrations (BPSs), congenital lobar emphysema, and bronchogenic cysts (Fig. 118.5). The reported incidence of CPAM is 9 per 100,000 live births, with prenatal diagnosis by fetal US most commonly coinciding with the 18–20-week anatomy scan. CCAMs are caused by abnormal branching and hamartomatous growth of the terminal respiratory structures, resulting in cystic and adenomatoid malformations (see Chapter 444), and are the most common congenital lung lesion. CCAMs

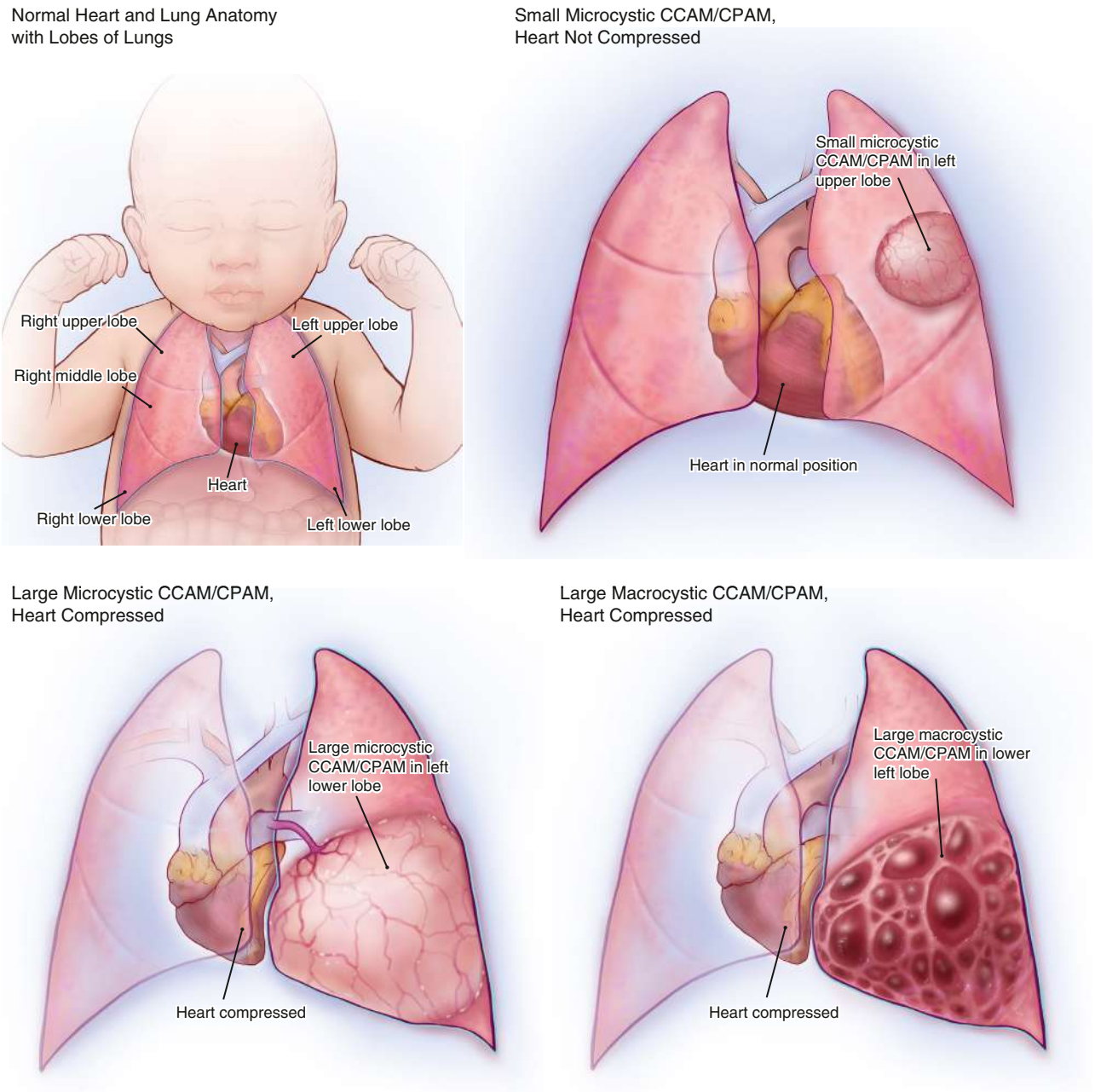

Fig. 118.5 Different types of congenital cystic adenomatoid malformation (CCAM)/congenital pulmonary airway malformation (CPAM), and how the different sizes and presentations of lung lesions can impact the heart and lungs. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

have been classified as microcystic (maximal cyst diameter <5 mm) vs macrocystic (≥5 mm), and prognosis is correlated with lesion size as well as presence of macrocysts (see Fig. 118.5). In contrast, BPSs appear as echogenic homogeneous masses on US and can be distinguished from CCAM by US evidence of systemic aortic arterial blood supply.

Large CPAMs may cause significant pulmonary hypoplasia and polyhydramnios due to decreased fetal swallowing secondary to esophageal compression. In severe cases, hydrops fetalis may result due to compression of the heart and great vessels. Hydrops with concomitant placentomegaly may result in maternal mirror syndrome, which is postulated to result from the release of vasoactive substances from the inflamed and edematous placenta. Due to the variable natural history of these lesions, a prenatal prognostic parameter, the CPAM volume ratio (CVR), is followed. The CVR is an index that compares the volume of the CPAM to the fetal head circumference. Most studies indicate >95% survival in CPAM patients with no hydrops and CVR <1.6, with greater risk for hydrops and need for closer surveillance in patients with a CVR >1.6.

Management of pregnancies complicated by prenatal diagnosis of a fetal lung lesion requires a plan for safe delivery. In the absence of mediastinal shift or flattening, small microcystic lesions will typically meet criteria for community delivery with a plan for close postnatal follow-up. Due to the risk of recurrent infection and malignant transformation, elective postnatal resection is anticipated; a CT angiogram (CTA) is performed at 4-6 weeks of age with surgical intervention following a few weeks later, when the potential for compensatory growth of the remaining lobe(s) is maximized. In the example of large macrocystic lesions with concern for respiratory compromise, delivery at an experienced center with access to ECMO and advanced emergent resection approaches is critical. For large lesions with CVR >1.6 or associated hydrops, the presence of macrocysts permits fetal thoracentesis and eventual thoracoamniotic shunt placement, which may reverse hydrops and allow continuation of the pregnancy without open fetal surgical intervention. Irrespective of the presence of drainable cysts, large lesions with threatened hydrops are treated with maternal betamethasone, which has been shown to reduce lesion size and reverse hydrops and may be given in multiple courses

to maximize therapeutic impact. Lesions not responsive to steroids or amenable to drainage may require open fetal surgery if the gestational age is less than 32 weeks; beyond 32 weeks' gestation, early delivery by C-section or ex utero intrapartum therapy (EXIT) with planned immediate resection is recommended.

CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME

Congenital high airway obstruction syndrome (CHAOS) is secondary to partial or complete intrinsic fetal upper airway obstruction. Most often due to laryngeal or tracheal atresia, CHAOS prevents lung fluid efflux resulting in dilated distal pulmonary airways and enlargement of the fetal lungs with potential for cardiac compression and the development of fetal hydrops. The diagnosis is confirmed by fetal MRI (Fig. 118.6).

In addition to CHAOS, extrinsic compression of the airway may be secondary to mass lesions (lymphangioma, teratoma, goiter) making respiratory efforts after birth difficult.

EXIT (ex utero intrapartum treatment) is a procedure to secure an airway during elective delivery (while the umbilical cord is patent and connected to the placenta), by C-section, before the onset of labor and before the fetus attempts to breathe (Fig. 118.7). The EXIT to airway procedure may be performed by direct laryngoscopy and

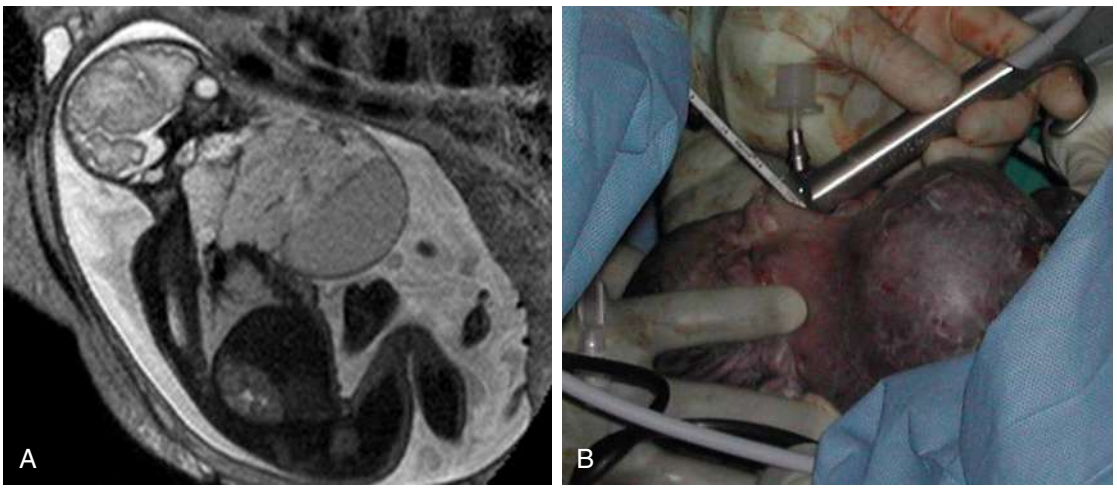

Fig. 118.6 A, Ultrafast MRI of fetus with giant cervical teratoma showing polyhydramnios and hyperextension of the neck. B, Fetus with giant cervical teratoma at the time of intubation by direct laryngoscopy and rigid bronchoscopy. *(From Lazar DA, Olutoye OO, Moise KJ, et al. Ex-utero intrapartum treatment procedure for giant neck masses – fetal and maternal outcomes. J Pediatr Surg. 2011;46:817–822, Fig. 1.)*

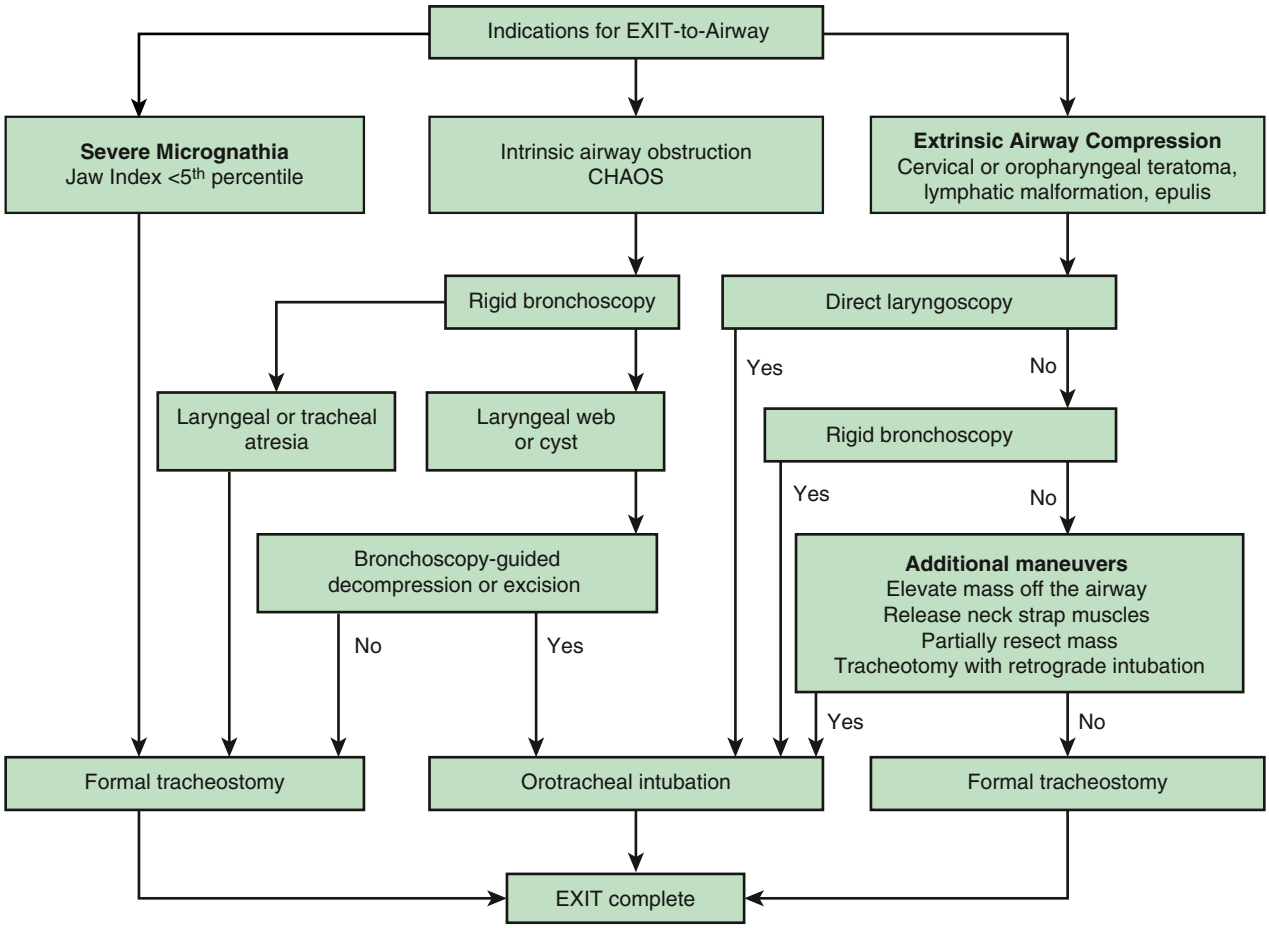

Fig. 118.7 Fetal airway management algorithm for ex utero intrapartum therapy (EXIT) procedures. Yes, Successful; No, not successful; CHAOS, congenital high airway obstruction syndrome. *(Adapted from Chatterjee D, Crombleholme TM. Airway management in EXIT procedures. In Jagannathan N, Fiadjoe JE, eds. Management of the Difficult Pediatric Airway. Cambridge, UK: Cambridge University Press; 2020.)*

endotracheal intubation or, if needed, rigid bronchoscopy, fiberoptic intubation, or tracheostomy (see Fig. 118.6).

SACROCOCCYGEAL TERATOMA

Sacrococcygeal teratoma (SCT) is one of the most common solid tumors of the newborn, with an incidence of 4.8 per 100,000 live births. This germline tumor has a female predominance (4:1) and is rarely associated with other congenital anomalies including nervous, skeletal, and cardiac abnormalities.

The high morbidity and mortality associated with SCT is multifactorial and is associated with both high rates of preterm delivery as well as hemodynamic sequelae. The mechanism of preterm delivery in SCT is believed to be a result of polyhydramnios-associated uterine irritability and premature rupture of membranes. Rupture of the tumor itself is rare but is most often fatal. The vascular composition of the tumor has hemodynamic implications for the fetus/newborn as high-output cardiac failure results from arteriovenous shunting causing vascular steal away from the placenta and the fetus to the SCT and compromised perfusion. Hydropic fetuses with placentomegaly may develop maternal mirror syndrome mandating immediate delivery. Prenatal diagnosis relies on US to identify the lesion and subsequent fetal MRI and echocardiography to assess for placental size, hydrops, and cardiac output physiology. Specific echocardiographic and Doppler US measurements of prognostic utility include cardiac output, cardiac/thoracic ratio, placental thickness, amniotic fluid index, and markers of hydrops including ascites as well as skin and scalp edema.

Given the morbidity and mortality associated with open fetal resection, prenatal intervention is limited to fetuses with mostly external masses manifesting hydrops and fetal cardiac insufficiency. The fetal approach to SCT debulking involves incision of the fetal skin circumferentially around the base of the tumor, application of a Rummel tourniquet, and debulking of the mass with a tissue stapler or energy device to interrupt the high output state (Fig. 118.8). Completion resection of the tumor and coccyx is performed postnatally. More often in the setting of early signs of evolving hydrops in the third trimester, early delivery (28-29 weeks' gestation) and debulking are considered with a similar strategy of staged debulking followed by completion resection when the neonate has stabilized. Resection of the coccyx is critical to avoid recurrence.

Reports of noninvasive interruption of blood flow with laser ablation, radiofrequency ablation, or vascular coiling are tempting but have been complicated by the inability to control the energy source leading to destructive tissue injury and injury to adjacent structures.

MYELOMENINGOCELE

Myelomeningocele (MMC) is the most common neural tube defect with an incidence of 1-2 per 1,000 live births. The disease is characterized by an abnormal outgrowth of the nerve root through the meninges with a concomitant vertebral bone and skin defect resulting in neural tissue exposure to the amniotic fluid. Associated defects include Chiari II malformation, characterized by descent of the cerebellar vermis through the foramen magnum, medullary kinking, and obliteration of the cistern magna leading to brainstem herniation. Hydrocephalus complicates up to 85% of MMC patients and is a major source of long-term morbidity, with high rates of shunting of cerebrospinal fluid required in survivors. Dermoid cysts are also common and may require intervention. Developmental and cognitive impairment is prevalent and profound, and current estimates suggest rates between 60% and 70% of pregnancies complicated by a prenatal diagnosis of MMC end in termination or demise. The etiology of MMC is likely multifactorial, with folic acid deficiency as well as use of folic acid antagonists associated with the development of neural tube defects. Screening for neural tube defects includes measurement of maternal serum α-fetoprotein (MSAFP) and US. Expectant mothers with screening concerns for MMC should be evaluated at a specialized center with further anatomic US, genetic screening, and ultrafast fetal MRI. In addition to identification of the neural tube defect, expert US can assess lower extremity function, and fetal MRI can define the extent of hindbrain herniation and ventricular size.

Before the introduction of fetal repair of MMC, fetal surgery was limited to life-threatening anomalies with high predictive mortality for the fetus or infant without intervention. However, a growing body of data suggested that the neurologic outcome in MMC was directly related to progressive injury from ongoing damage to the exposed spinal cord during pregnancy (see Chapter 631.3) (Fig. 118.9). A large multicenter National Institutes of Health–sponsored Management of Myelomeningocele Study (MOMS) comparing the safety and efficacy of prenatal repair of MMC with that of standard postnatal repair was performed and determined a clear advantage for prenatal surgery before 26 weeks' gestation. The MOMS trial demonstrated a significant reduction in the need for ventriculoperitoneal (VP) shunt at 12 months in the fetal repair group (40% vs 82% in postnatal repair group) with reduced hindbrain herniation and improved mental development and motor function at 30 months. Furthermore, the need for shunting was independent of lesion level and degree of hindbrain herniation. The 1-year neurosurgical outcomes for the complete cohort showed that prenatal surgery did not decrease the need for shunting in those fetuses with a cerebral ventricular size of ≥15 mm at initial screening. Prenatal surgery was associated with an increased risk for earlier gestational age at birth. Delivery occurred before 30 weeks of gestation in 11% of neonates that had fetal MMC repair. Adverse pulmonary sequelae were rare in the prenatal surgery group despite an increased rate of oligohydramnios. The benefits of prenatal surgery outweigh the complications of prematurity.

Open fetal repair of MMC has been a paradigm-shifting advance in fetal surgery and has led to the formation of the North American Fetal Therapy Network (NAFTNet) registry of fetal MMC patients, with follow-up studies continuing to demonstrate the benefits

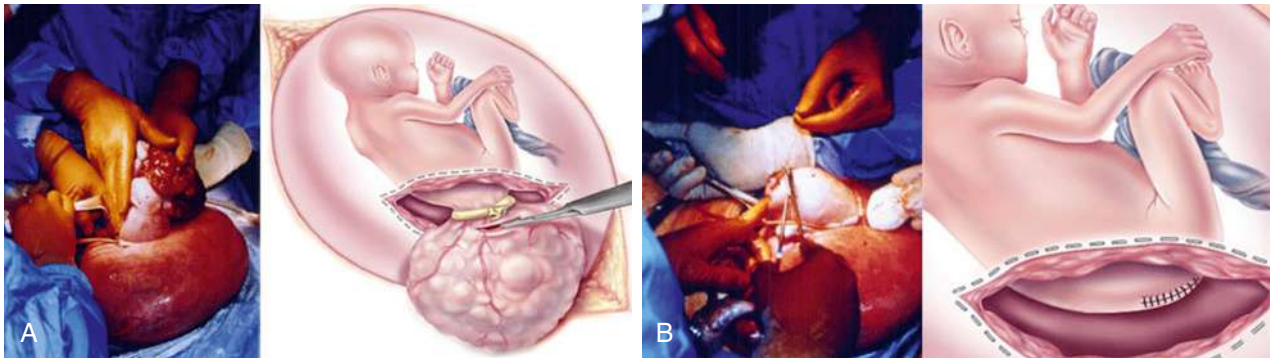

Fig. 118.8 A, Exposure of 26-week fetus through hysterotomy revealing sacrococcygeal teratoma (SCT). B, Closure of skin flaps after resection. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

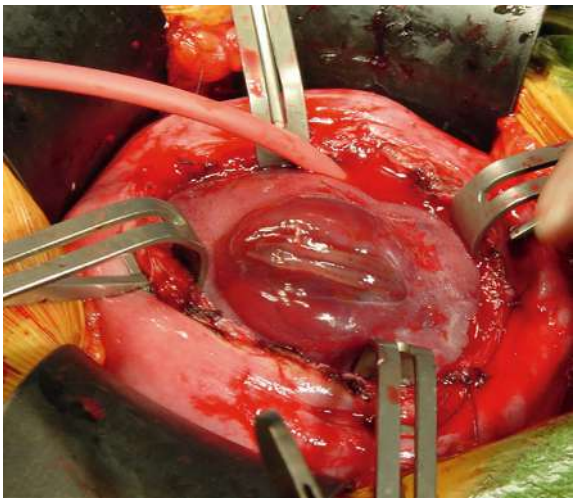

Fig. 118.9 Open fetal myelomeningocele repair. *(From Hirose S, Harrison MR. Fetal therapy. In Holcomb GW III, Murphy JP, eds. Ashcraft's Pediatric Surgery. 5th ed. St Louis: Elsevier; 2010. Fig. 10-5.)*

Fig. 118.10 In twin-to-twin transfusion syndrome (TTTS), blood flow through vascular connections on the surface of the placenta is unequal. One twin ("donor twin") pumps blood to the other twin ("recipient"). This unequal blood flow between twins results in the recipient twin *(right)* having too much amniotic fluid, and donor twin *(left)* with little or no amniotic fluid. *(Copyright 2021, The Children's Hospital of Philadelphia.)*

observed in the MOMS trial in subsequent series. The risk of prematurity and requirement for cesarean section deliveries for all future pregnancies remain significant considerations for this procedure. The less invasive *fetoscopic* MMC repair approach, which is being developed at a limited number of centers, may reduce maternal morbidity and prematurity rates associated with open fetal MMC repair, but this remains a question of active ongoing investigation. At this time, fetoscopic fetal MMC repair is recommended in an investigational setting according to the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.

TWIN-TO-TWIN TRANSFUSION SYNDROME

Twin-to-twin transfusion syndrome (TTTS) is a condition that affects approximately 10–15% of *monochorionic diamniotic identical twin* pregnancies. In these cases, shared fetoplacental circulation can lead to unbalanced blood flow between the two fetuses which, left untreated, results in perinatal loss of one or both fetuses in approximately 80% of cases (Fig. 118.10). Unlike dichorionic twins, which do not have any vascular connections between the placentas, monochorionic twins have vascular anastomoses within the shared fetoplacental circulation. Unbalanced deep arteriovenous anastomoses without proper compensation from the superficial bidirectional vessels results in discordant blood supply, with the "donor" fetus presenting with oligohydramnios and intrauterine growth restriction while the "recipient" fetus develops polyhydramnios, heart failure, and hydrops due to hypervolemia. Neurodevelopmental delay is commonly observed in long-term survivors.

TTTS is usually a gradual process that is usually observed in the second trimester. Diagnosis is performed via US in the second trimester. The Quintero classification system is used to stratify TTTS into five stages.

- Stage I: Abnormal amniotic fluid levels (oligo- and polyhydramnios) with bladder filling in the donor twin
- Stage II: Features of stage I with collapsed bladder in the donor twin
- Stage III: New abnormal flow through the umbilical artery or ductus venosus in either the donor or recipient twin with stage II features present
- Stage IV: Hydrops in either the donor or recipient twin
- Stage V: Intrauterine demise of either the donor or recipient twin

Several therapies have been proposed for the treatment of TTTS. Amnioreduction is performed to remove excess fluid from the sac with polyhydramnios and can be done serially to help prevent preterm later. Endoscopic or fetoscopic laser ablation of the superficial vascular anastomoses is another therapeutic option. Under local or regional anesthesia, a trocar is placed under US guidance and an endoscope passed, through which superficial anastomoses are then identified and coagulated, followed by amnioreduction. The procedure is performed only once during the pregnancy, usually prior to 26 weeks. Several observational studies have noted perinatal survival approximating 60% with both amnioreduction and laser coagulation. A multicenter randomized trial demonstrated a survival and neurologic advantage after laser coagulation therapy vs amnioreduction; although after 26 weeks, amnioreduction is often still recommended for technical reasons. Other surgical therapies include septostomy (disrupting the membrane between the twins) and selective umbilical cord coagulation in severe cases. Like amnioreduction, septostomy does not alter the underlying pathophysiology. All cases should be referred to tertiary care centers with extensive experience in the treatment of TTTS.

OTHER INDICATIONS

Antenatal intervention for **cardiac defects**, such as aortic stenosis, pulmonic stenosis, and hypoplastic left heart syndrome (HLHS), have been used to dilate, with balloon valvuloplasty, stenotic valves (aortic stenosis) to prevent further development of HLHS (creating biventricular physiology) (Fig. 118.11) (see Chapter 480.10).

Laser therapy has been used to treat TTTS (Chapter 119.1) and amniotic bands (Fig. 118.12).

FETAL CENTERS

The value of fetal surgical program centers extends beyond fetal intervention itself. Often, families will present to a fetal center with a new diagnosis and little understanding of the implications for their baby and family. Prenatal counseling by the fetal team provides the opportunity to confirm the diagnosis, investigate for other anomalies and genetic susceptibilities, and provide detailed counseling to achieve understanding of both the diagnosis and

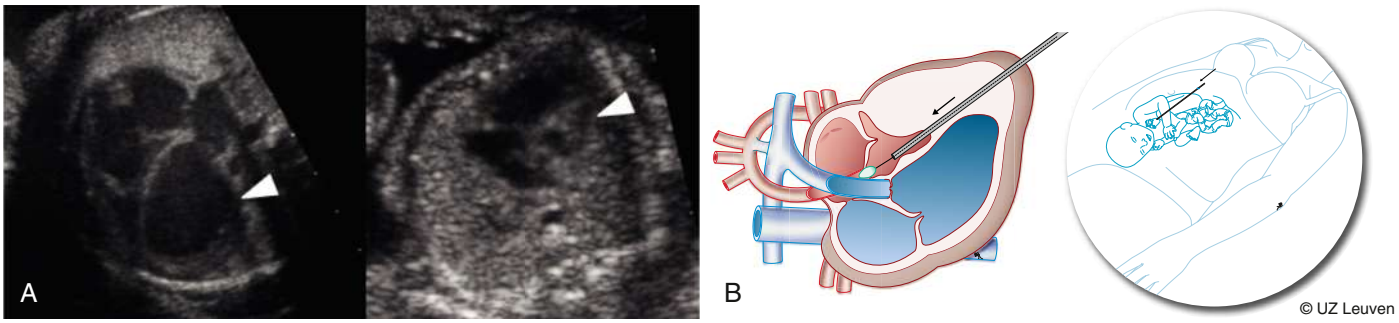

Fig. 118.11 **A,** Ultrasound image *(right panel)* is a cross section at the level of the fetal chest, demonstrating the four-chamber view in a fetus with aortic stenosis. Notice that the left ventricle *(arrowhead)* is dilated. Dilation occurs before the development of hypoplasia, which can be seen *(arrowhead)* in another fetus *(left panel)*. **B,** Schematic representation of percutaneous valvuloplasty, in this case of the left ventricular outlet tract. (***A*** *from van Mieghem T, Baud D, Devlieger R, et al. Minimally invasive fetal therapy. Best Pract Res Clin Obstet Gynaecol 2012;26:711–725;* ***B*** *copyright UZ Leuven, Leuven, Belgium.)*

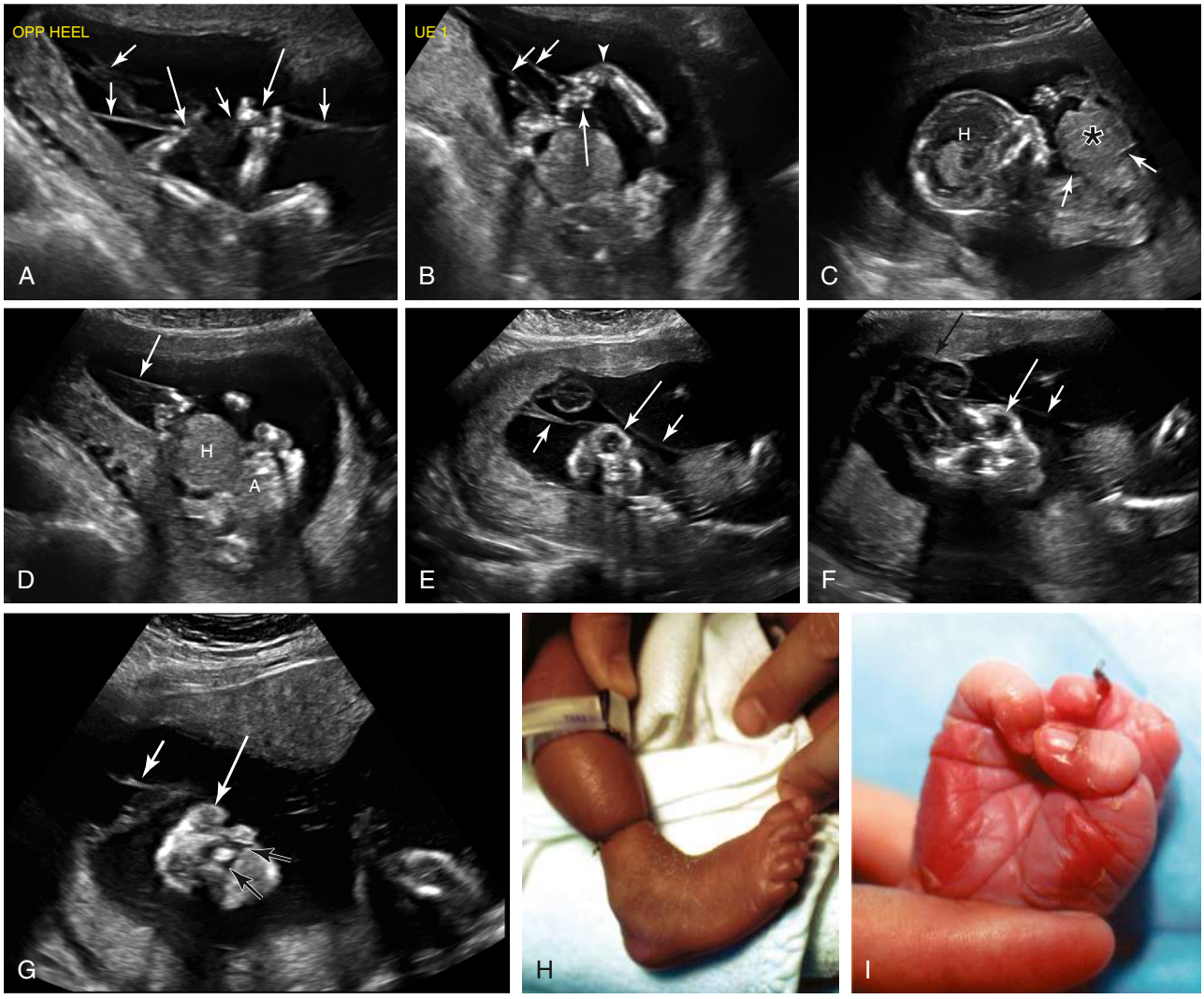

Fig. 118.12 Amniotic band sequence in two different fetuses. **A** and **B,** Effects on the extremities. Limbs of a fetus with amniotic band sequence show multiple amniotic bands (*short arrows,* **A** and **B**), amputation of fingers and toes (*long arrows,* **A** and **B**), and a fixed deformity of the hand at the wrist (*arrowhead,* **B**). **C** and **D,** Effects on the thorax and abdomen of the same fetus as in **A** and **B.** Sagittal image **(C)** shows a thoracoabdominal wall defect *(arrows)* with a large amount of herniated abdominal and thoracic contents *(asterisk)* outside the body. *White H,* Head. **D,** Axial image of the fetal abdomen **(A)** confirms the presence of a large ventral abdominal hernia *(H),* in the setting of amniotic bands *(arrow).* **E** to **G,** Effects on craniofacial structures in a different fetus. **E,** Coronal image of face shows multiple amniotic bands *(short arrows)* and nonvisualization of the calvarium. This results in a craniofacial appearance that resembles anencephaly *(long arrow).* **F,** A large encephalocele *(black arrow)* is seen above the level of the orbits *(long white arrow)* in a different scan plane. An amniotic band *(short white arrow)* is also seen. **G,** Coronal image of anterior portion of face shows facial clefts *(black arrows)* due to amniotic bands. *Short white arrow,* Amniotic band; *long white arrow,* orbits. **H,** Band constricting the ankle, leading to deformational defects. **I,** Pseudosyndactyly, amputation, and disruption of finger morphogenesis. (***A-G*** *from Hertzberg BS, Middleton WD. Ultrasound: The Requisites. 3rd ed. Philadelphia: Elsevier; 2016. Figs. 19-22;* ***H*** *and* ***I*** *from Jones KL, Smith DW, Hall BD, et al. A pattern of craniofacial and limb defects secondary to aberrant tissue bands. J Pediatr. 1974;84:90–95.)*

Table 118.3 Selection of Patients for Fetal Repair

LEVEL OF CERTAINTY	DIAGNOSIS
DIAGNOSTIC CERTAINTY/PROGNOSTIC CERTAINTY	
Genetic problems	Trisomy 13, 15, or 18 Triploidy
Central nervous system abnormalities	Anencephaly/acrania Holoprosencephaly Large encephaloceles
Heart problems	Acardia Inoperable heart anomalies
Kidney problems	Potter syndrome/renal agenesis Multicystic/dysplastic kidneys Polycystic kidney disease
DIAGNOSTIC UNCERTAINTY/PROGNOSTIC CERTAINTY	
Genetic problems	Thanatophoric dwarfism or lethal forms of osteogenesis imperfecta
Early oligo/anhydramnios and pulmonary hypoplasia	Potter syndrome with unknown etiology
Central nervous system abnormalities	Hydranencephaly
	Congenital severe hydrocephalus with absent or minimal brain growth
Prematurity	<23 weeks' gestation
PROGNOSTIC UNCERTAINTY/BEST INTEREST	
Genetic problems	Errors of metabolism that are expected to be lethal even with available therapy
Mid oligo/anhydramnios	Renal failure requiring dialysis
Central nervous system abnormalities	Complex or severe cases of meningomyelocele Neurodegenerative diseases, such as spinal muscular atrophy
Heart problems	Some cases of hypoplastic left heart syndrome Pentalogy of Cantrell (ectopia cordis)
Other structural anomalies	Some cases of giant omphalocele Severe congenital diaphragmatic hernia with hypoplastic lungs Idiopathic nonimmune hydrops Inoperable conjoined twins Multiple severe anomalies
Prematurity	23-24 weeks' gestation

From Leuthner SR. Fetal palliative care. *Clin Perinatol* 2004;31:649–665. Table 1.

all available treatment options. This collaborative and multidisciplinary family-centered approach allows for the development of a management plan that may include fetal surgery or intervention, enhanced monitoring of the fetus and mother, and coordination of complex deliveries involving multidisciplinary delivery teams and specialized equipment as required for EXIT to ECMO, EXIT to airway, EXIT to tumor resection, delivery to cardiac catheterization, and procedures on placental support.

In some highly specialized fetal centers, delivery may be facilitated with the neonatal intensivists, perinatal anesthesiologist, and pediatric surgical care teams present in the same location to permit expert stabilization and resuscitation of the neonate. The benefits range from the psychological benefits of avoiding maternal-infant separation as well as improved outcomes in diagnoses such as CDH, in which early stabilization of the neonate is critical to minimize pulmonary hypertensive crisis.

Finally, but equally importantly, not all severely affected fetuses will have available therapies in utero or after birth. In these lethal situations, fetal care planning will provide support for the family and a plan for delivery room or nursery palliative care (Table 118.3) (see Chapter 8).

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Chapter 119

The High-Risk Infant

Erik Brandsma, Lori A. Christ, and Andrea F. Duncan

The term *high-risk infant* designates an infant at greater risk for neonatal morbidity and mortality; many factors can contribute to an infant being high risk (Table 119.1). There are four broad categories of high-risk infants: the preterm infant, infants with special healthcare needs or dependence on technology, infants at risk because of family issues, and infants with anticipated early death.

Table 119.1 Factors in Considering Infants as High Risk for Morbidity or Mortality in the Neonatal Period

BIRTH PARENT DEMOGRAPHIC FACTORS
Maternal age <16 yr or >40 yr
Environmental, economic, social disadvantage, racial discrimination
BIRTH PARENT MEDICAL HISTORY
Genetic disorders
Diabetes mellitus
Hypertension
Asymptomatic bacteriuria
Rheumatologic illness (systemic lupus erythematosus)
Immune-mediated diseases
Long-term medication (see Chapters 117.4 and 117.5)
PREVIOUS PREGNANCY
Intrauterine fetal demise
Neonatal death
Prematurity
Intrauterine growth restriction
Congenital malformation
Incompetent cervix
Blood group sensitization, neonatal jaundice
Neonatal thrombocytopenia
Hydrops
Inborn errors of metabolism
PRESENT PREGNANCY
Vaginal bleeding (abruptio placentae, placenta previa)
Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)
Multiple gestation
Preeclampsia
Premature rupture of membranes
Short interpregnancy time
Poly-/oligohydramnios
Acute medical or surgical illness
Familial or acquired hypercoagulable states
Abnormal fetal ultrasonographic findings
Treatment of infertility
Inadequate prenatal care
Substance use disorder
LABOR AND DELIVERY
Premature labor (<37 wk)
Postdates pregnancy (≥42 wk)
Fetal distress
Breech presentation
Meconium-stained fluid
Nuchal cord
Cesarean delivery
Forceps or vacuum assisted delivery
Apgar score <4 at 5 min
NEONATE
Birthweight <2,500 g or >4,000 g
Birth <37 wk or ≥42 wk of gestation
Small or large for gestational age
Respiratory distress, cyanosis
Congenital malformation
Pallor, plethora, petechiae

All high-risk infants require closer evaluation and/or treatment by experienced physicians and nurses. This often starts before delivery and continues in the delivery room and through a neonatal intensive care unit (NICU) stay (see Chapter 121). Regionalized care for infants is based on the acuity of care that can be provided at hospitals with different levels of care and whether transport should be undertaken (see Chapter 120). It is important to note that additional care does not stop at time of NICU discharge, and that many high-risk infants also benefit from additional resources and follow-up after discharge from the hospital (see Chapter 119.5).

Twins and higher-order multiples are at increased risk for morbidity and mortality and are discussed in Chapter 119.1, whereas other infants deemed high risk are discussed throughout this textbook. Preterm infants comprise the majority of high-risk infants. Approximately 15 million infants are born preterm (before 37 weeks' gestational age) each year worldwide, accounting for about 1 in every 10 babies born. The World Health Organization (WHO) defines infants born before 28 weeks' gestational age as *extremely preterm* infants, infants born between 28 and 31 6/7 weeks as *very preterm* (see Chapter 119.2), and infants born between 32 and 36 6/7 weeks as *moderate to late preterm* infants (see Chapter 119.3). Risk of both morbidity and mortality increases with earlier gestational age. Gestational age, birthweight, and gender are all important factors that impact neonatal mortality (Fig. 119.1). The **highest risk** of neonatal and infant mortality occurs in infants with birthweight <1,000 g and/or with gestational age <28 weeks. The **lowest risk** of neonatal mortality occurs in infants with birthweight of 3,000-4,000 g and a gestational age of 39-41 weeks. As birthweight increases

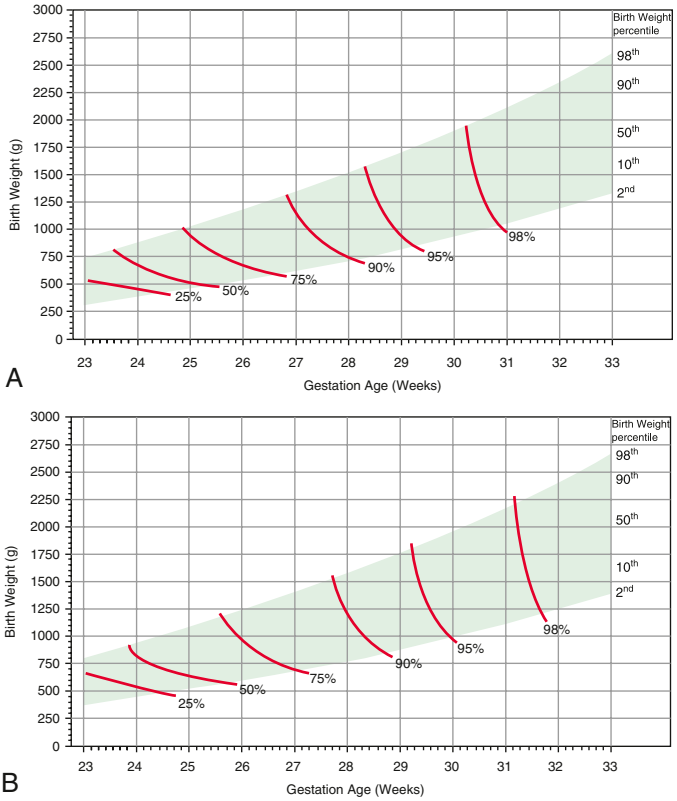


Fig. 119.1 Contour plot of predicted survival according to gestational age, birthweight, and gender. **A**, Female. **B**, Male. The contour lines join combinations of gestational age and birthweight of equal estimated probability of survival. Birthweight percentiles are shown for information. Data based on singleton infants born in the United Kingdom between January 2008 and December 2010 who survived to NICU admission. *(From Manktelow BN, Seaton SE, Fields DJ, et al. Population-based estimates of in-unit survival for very preterm infants. Pediatrics. 2013;131:e425e432. Fig. 2.)*

from 400 to 3,000 g and gestational age increases from 23 to 39 weeks, a logarithmic decrease in neonatal mortality occurs. Once birthweight exceeds 4,000 g and/or gestational age exceeds 42 weeks, the incidence of neonatal morbidities and mortality increases (see Chapter 119.4).

119.1 Multiple-Gestation Pregnancies

Lori A. Christ

CLASSIFICATION OF TWINS

Monozygotic vs Dizygotic Twins

Traditionally, twins have been classified as either **monozygotic** (originating from one ovum fertilized by one sperm in a single fertilization event that then results in postzygotic division of the conceptus into two embryos) or **dizygotic** (originating from two fertilization events each occurring when a single ovum is fertilized by a single sperm). Identifying twins as monozygotic or dizygotic is useful in determining the relative influence of heredity and environment on human development and disease. Detailed blood typing, gene analysis, or tissue (human leukocyte antigen) typing can be used for zygosity testing (an exception being blood typing in cases of **chimeric** twins, where one or both twins contain distinct cell lines from multiple zygotes). While often referred to as "identical" twins, physical and cognitive differences may still exist between monozygotic twins due to differences in the in utero environment, the mitochondrial genome, in posttranslational gene product modification, or in the epigenetic modification of nuclear genes in response to environmental factors.

Chorionicity and Amnionicity

Twins can also be classified by the number of chorions and amnions in the pregnancy. Dizygotic twins largely result in **dichorionic, diamniotic** pregnancies, although rarely may result in atypical twinning (see later). The chorionicity and amnionicity of monozygotic twins depends on the timing of fission of the zygote. One-third of monozygotic twins are dichorionic and diamniotic, and result from splitting on embryonic day 1-3. **Monochorionic**, diamniotic twins result from splitting on embryonic day 3-8, and monochorionic, **monoamniotic** twins result from splitting on day 8-13. Determination of amnionicity and chorionicity are not reliable ways of determining zygosity. An apparently single placenta may be present with either monozygotic or dizygotic twins, but inspection of a dizygotic placenta usually reveals that each twin has a separate chorion that crosses the placenta between the attachments of the cords and two amnions. Separate or fused dichorionic placentas may be disproportionate in size, resulting in growth restriction or malformation of the fetus attached to the smaller placenta or the smaller portion of the placenta.

Incidence

Differences in the incidence of twins worldwide mainly involve dizygotic twins, as monozygotic twinning appears to be independent of heritable factors. In 2019 the U.S. final natality report recorded a twin rate of 32.1 per 1,000 live births, which has continued to decline after an all-time high in 2014. Increases in monozygotic and dizygotic twinning had been associated with advanced maternal age (AMA) and the use of assisted reproductive technologies (ARTs). The rate of triplets and higher-order multiple births was 87.7 per 100,000 live births in the United States and has continued to decline since 1998. The use of single-embryo transfer in ART has decreased the numbers of triplet births and higher-order multiples.

ETIOLOGY

Dizygotic twins result from polyovulation, or the release of more than one ovum at a single ovulation. Polyovular pregnancies are more frequent after the second pregnancy, with increasing maternal age, and in families with a history of dizygotic twins. They may result from simultaneous maturation of multiple ovarian follicles, but follicles containing two ova have also been described as a genetic trait leading to twin pregnancies. Twin-prone women have higher levels of gonadotropin. Polyovular pregnancies occur in many women treated for infertility with ovarian stimulants such as clomiphene or gonadotropins.

The etiology of monozygotic twinning is unknown, but there are two prevailing theories. In the classic **fission theory**, twinning results from the splitting of a single conceptus, with the timing of splitting resulting in differing amnionicity and chorionicity (i.e., the earlier the fission occurs, the more likely the twins are to be diamniotic dichorionic) (Fig. 119.2). However, this theory fails to account for several forms of atypical twinning, including the occurrence of **diamniotic dichorionic monozygotic** twinning after single-embryo transfer in the

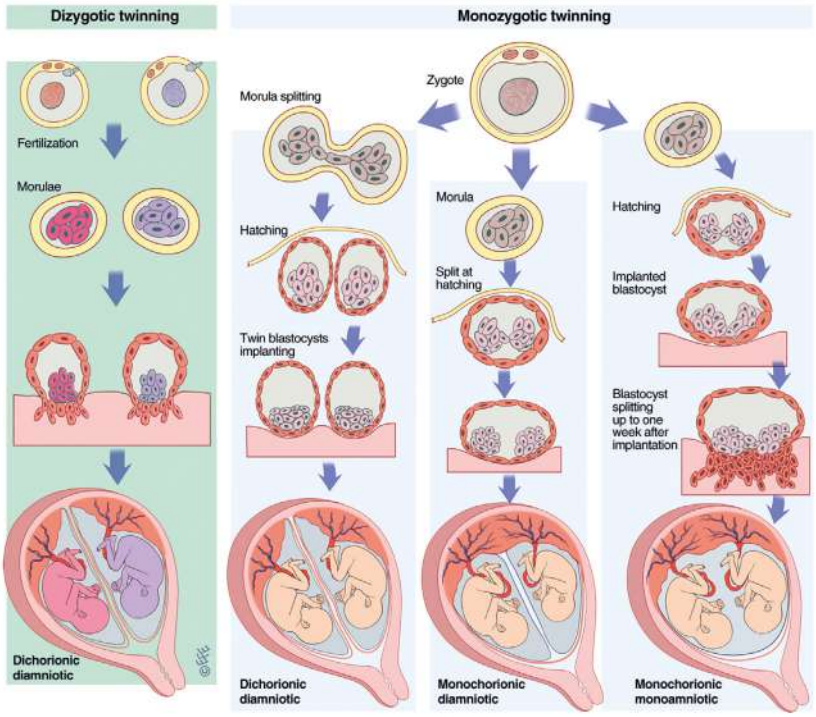


Fig. 119.2 Classical fission theory of twinning. Dizygotic twins result from two distinct fertilization events, with dichorionic diamniotic twins each developing to become a genetically distinct individual. Monozygotic twins result from postzygotic splitting of the product of a single fertilization event. Splitting on days 1-3 (up to the morula stage) results in dichorionic diamniotic twins, on days 3-8 (during which blastocyst hatching occurs) in monochorionic diamniotic twins, on days 8-13 in monochorionic monoamniotic twins. *(Illustration copyright LeventEfe, CMI. www.leventefe.com.au.)*

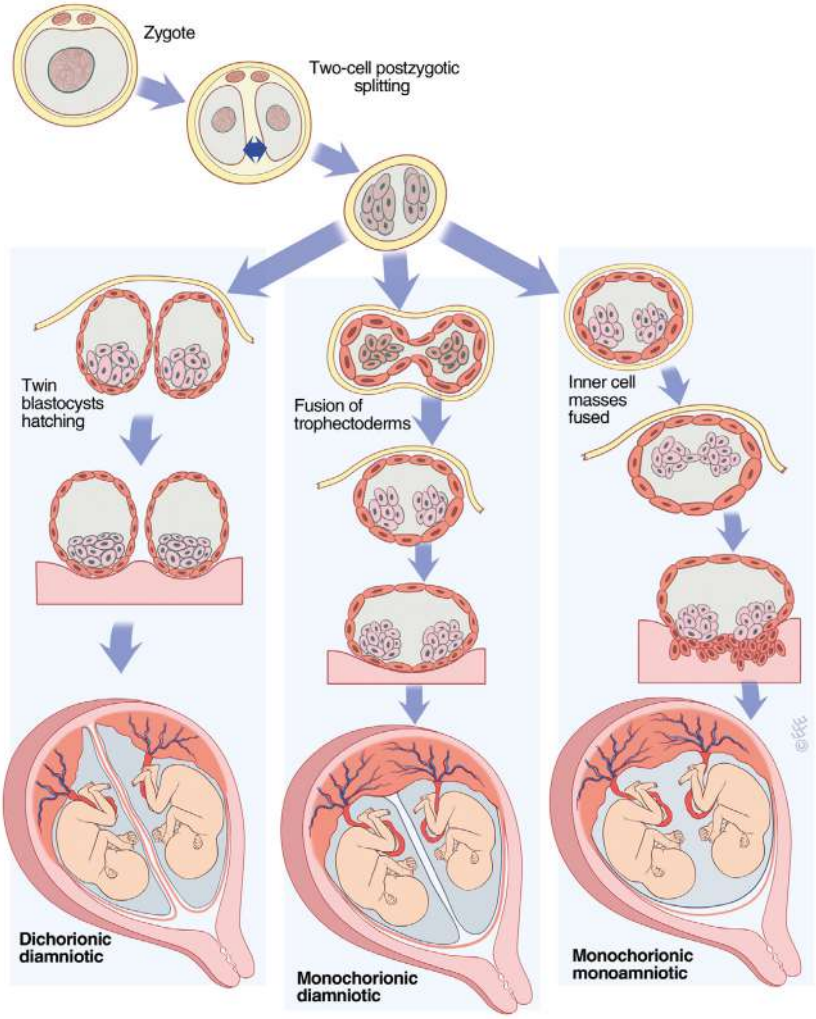


Fig. 119.3 Fusion theory of monozygotic twinning. Splitting occurs at the postzygotic two-cell stage, with each cell forming a distinct individual. If twin blastocysts hatch from the zona pellucida together, dichorionic diamniotic twins will result. If the two trophectoderms fuse before hatching and the inner cell masses are separated within the shared trophectoderm, monochorionic diamniotic twins will result. If the inner cell masses are fused and separated later, monochorionic monoamniotic twins will result. *(Illustration copyright LeventEfe, CMI. www.leventefe.com.au)*

late blastocyst state, phenotypically discordant monozygotic twins, and asymmetrically attached conjoined twins. An alternate **fusion theory** of twinning has been proposed to account for this discrepancy, in which the inner cell masses of trophectoderm fuse after the initial two-cell splitting stage (Fig. 119.3).

Atypical Twinning

Conjoined twins occur in 1 in 50,000 pregnancies and 1 in 250,000 live births. Theoretically, they result from later fission of a single zygote (10-14 days) or from fusion of two zygotes (as proposed for asymmetrically attached conjoined twins). Most conjoined twins are female. The prognosis for symmetrically conjoined twins depends on the possibility of surgical separation, which in turn depends on the extent to which vital organs are shared. The site of connections varies, as follows: thoracoomphalopagus (28% of conjoined twins), thoracopagus (18%), omphalopagus (10%), craniopagus (6%), and incomplete duplication (10%). The term *parasitic twin* has historically been used to describe the smaller and less completely developed member of a pair of conjoined twins; this twin has typically had embryonic demise but remains vascularized by the surviving *independent* twin (the **autocyte**). For asymmetrically attached conjoined twins in whom one twin is dependent on the cardiovascular system of the intact autocyte (**exoparasitic twins**, 1 in 1 million live births) survival of the autocyte depends on the feasibility of excising the *exoparasitic* twin. For **endoparasitic twins** (*fetus in fetu,* 1 in 500,000 live births) in whom one (or more) fetus exists as a benign mass in the autocyte, survival of the autocyte is unaffected. **Superfecundation,** or fertilization of an ovum by an insemination that takes place after one ovum has already been fertilized, and **superfetation**, or fertilization and subsequent development of an embryo when a fetus is already present in the uterus, have been proposed as explanations for differences in size and appearance of certain twins at birth.

Diagnosis

A prenatal diagnosis of pregnancy with twins is suggested by a uterine size that is greater than that expected for gestational age, auscultation of two fetal heartbeats, and/or elevated maternal serum α-fetoprotein (AFP) or human chorionic gonadotropin (hCG) levels. It is confirmed by ultrasonography. Physical examination of twins is necessary but not sufficient to determine zygosity of twins. In the event that congenital anomalies are present or there are transfusion or transplantation considerations, genetic testing of zygosity should be performed. Although noninvasive prenatal testing (NIPT) is becoming more common, the results should be interpreted with caution in multiple-gestation pregnancies until normative values are better established.

Complications

Twin and higher-order pregnancies are associated with poorer neonatal and perinatal outcomes compared with singleton pregnancies of the same gestation. Severe maternal morbidities and death are also

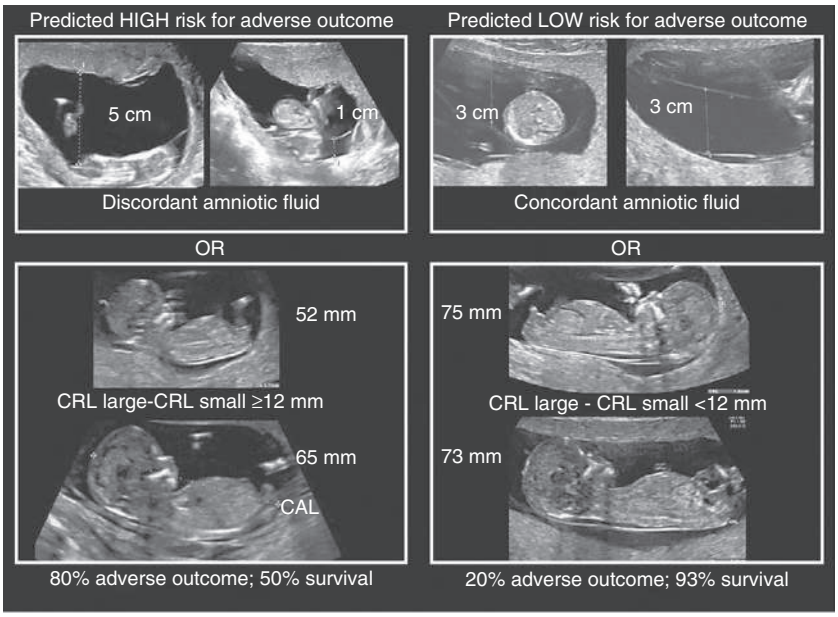


Fig. 119.4 Representation of first-trimester risk assessment for the development of discordant growth, twin-twin transfusion syndrome (TTTS), or intrauterine demise. Discordant amniotic fluid in the first trimester generally corresponded with deepest vertical pockets ≤3 cm in one sac and ≥6.5 cm in the other. Discordance in crown-rump length (CRL) was present if the difference was ≥12 mm. *(From Lewi L, Gucciardo L, Van Mieghem T, et al. Monochorionic diamniotic twin pregnancies: natural history and risk stratification. Fetal Diagn Ther. 2010;27:121–133.)*

twice as likely in twin pregnancies worldwide compared with singleton pregnancies.

Most twins are born prematurely, which contributes to additional neonatal and childhood morbidity and mortality. Spontaneous single intrauterine demise occurs at a rate of about 6% of all twin pregnancies. Twin-twin transfusion syndrome (TTTS) and early-onset discordant growth are associated with an overall worse prognosis (see Chapter 118). The perinatal mortality of twins is about four times that of singletons, with **monochorionic** twins being particularly at risk. **Monochorionic** twins have an increased risk of a demised twin in utero. The surviving twin has a greater risk for cerebral palsy and other neurodevelopmental sequelae. **Monoamniotic** twins have an increased likelihood of cord entanglement, which may lead to asphyxia. Twins are at greater risk for congenital malformations, with up to 25% of monozygotic twins being affected. Theoretically, the twin delivered second is at higher risk of anoxia than the first because the placenta may separate after birth of the first twin and before birth of the second. In addition, delivery of the second twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the first twin's birth.

Triplet or higher-order births are associated with an increased risk of death or neurodevelopmental impairment compared with extremely low birthweight (ELBW) singleton and twin infants after controlling for gestational age. The mortality for multiple gestations with ≥4 fetuses is excessively high for each fetus. Because of this poor prognosis, selective fetal reduction has been offered as a treatment option.

Twin-Twin Transfusion Syndromes

Placental vascular anastomoses occur with high frequency in **monochorionic** twins (see Chapter 118). In monochorionic placentas, the fetal vasculature is usually joined, sometimes in a very complex manner. They are usually balanced and neither twin is appreciably affected. Artery-to-artery communications cross over placental veins, and when anastomoses are present, blood can readily be stroked from one fetal vascular bed to the other. Vein-to-vein communications are similarly recognized but are less common. A combination of artery-to-artery and vein-to-vein anastomoses is associated with the condition of **acardiac fetus**. This rare lethal anomaly (1 in 35,000) is secondary to the **twin reversed arterial perfusion (TRAP) syndrome**. In utero radiofrequency or laser ablation of the anastomosis or cord occlusion can be used to treat heart failure in the surviving twin. However, death of the autocyte is reported in up to 75% of cases. In rare cases, one umbilical cord may arise from the other after leaving the placenta, and the twin attached to the secondary cord usually is malformed or dies in utero.

Table 119.2 Characteristic Changes in Monochorionic Twins with Uncompensated Placental Arteriovenous Shunts

TWIN ON:	
ARTERIAL SIDE—DONOR	**VENOUS SIDE—RECIPIENT**
Prematurity	Prematurity
Oligohydramnios	Polyhydramnios
Intrauterine growth restriction	Hydrops
Pale	Plethoric
Anemic	Polycythemic
Hypovolemic	Hypervolemic
Hypoglycemic	Cardiac hypertrophy
Microcardia	Myocardial dysfunction
Glomeruli small or normal	Glomeruli large Tricuspid valve regurgitation Right ventricular outflow obstruction
Arterioles thin walled	Arterioles thick walled

In **twin-twin transfusion syndrome (TTTS)**, an artery from one twin acutely or chronically delivers blood that is drained into the vein of the other. The latter develops polyhydramnios and polycythemia, and the former has oligohydramnios, anemia, and growth restriction (Fig. 119.4). TTTS is more common in monozygotic twins and affects up to 30% of monochorionic twins. Death of the donor twin in utero may result in generalized fibrin thrombi in the smaller arterioles of the recipient twin, possibly as the result of transfusion of thromboplastin-rich blood from the macerating donor fetus. Disseminated intravascular coagulation (DIC) may develop in the surviving twin. Table 119.2 lists the more frequent changes associated with a large shunt. Preterm birth and/or death of the surviving twin is also highly likely. **Treatment** of this highly lethal problem includes aggressive amnioreduction for polyhydramnios, selective twin termination, and most often, laser or fetoscopic ablation of anastomosis (Fig. 119.5).

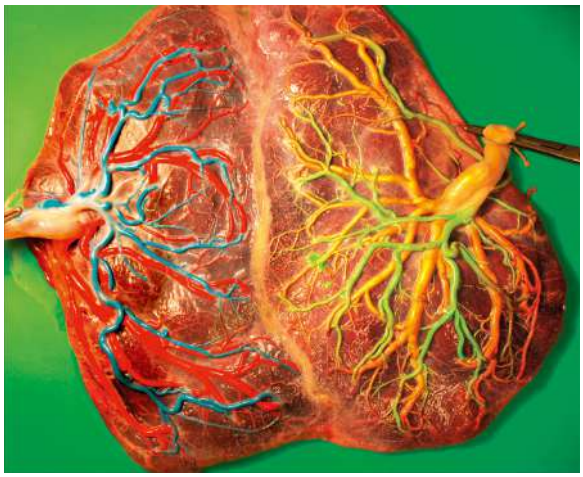
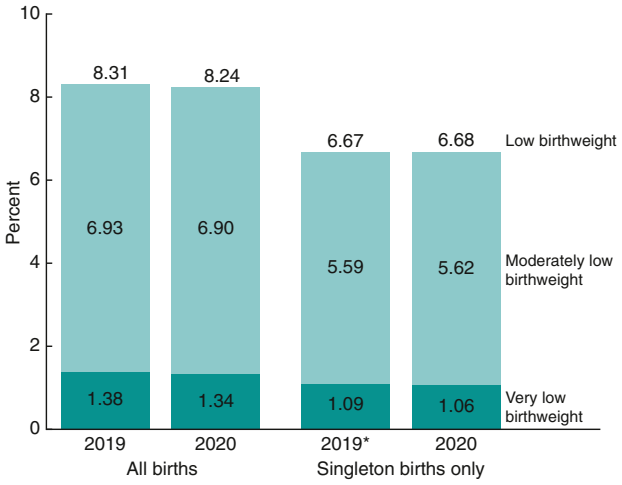


Fig. 119.5 Color-dye-stained twin-to-twin transfusion syndrome placenta that was treated using the Solomon technique. Blue and green dye are used to stain the arteries, and pink and yellow dye are used to stain the veins. After identification and coagulation of each individual anastomosis, the complete vascular equator is coagulated from one placental margin to the other. *(From Slaghekke F, Lopriore E, Lewi L, et al. Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomized controlled trial, Lancet. 2014;383:2144–2150. Fig. 3.)*



SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

Fig. 119.6 Total and singleton low birthweight rates: United States, 2019 and 2020. *Numbers do not add to total du to rounding. *(From Osterman M, Hamilton B, Martin JA, Driscoll AK, Valenzuela CP. Births: Final Data for 2020. Natl Vital Stat Rep. 2021;70[17]:1–50. Fig. 3.)*

Management

Prenatal detection of a multiple gestation pregnancy enables the obstetrician and pediatrician to anticipate complications. The risk of multiple-gestation pregnancies due to ART may be reduced by elective single-embryo transfers. Asymptomatic early cervical dilation may be managed with cerclage, which is 50% effective in preventing delivery before 28 weeks' gestation. Elective delivery of twins at 37 weeks (or earlier for **monochorionic**, **monoamniotic** twins) reduces the complication rate for the fetuses and the birth parent. Furthermore, in twin pregnancies between 32 and 39 weeks' gestation, planned vaginal delivery is preferred if the first twin is in the cephalic presentation. Close observation and attendance by a pediatric team are indicated in the immediate neonatal period so that prompt treatment of asphyxia or fetal transfusion syndrome can be initiated. The decision to perform an immediate blood transfusion in a severely anemic "donor" twin or a partial exchange transfusion of either twin due to anemia in the "donor" or polycythemia in the "recipient" twin must be based on clinical judgment.

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119.2 Extremely and Very Preterm Infants

Lori A. Christ and Erik Brandsma

Traditionally, the delivery date is determined 280 days after the last menstrual period (LMP). However, only 4% of pregnant women deliver at 280 days, and only 70% deliver within 10 days of the estimated delivery date.

Infants born before 37 weeks from the first day of the LMP are termed *premature* by WHO. Infants born before 28 weeks' gestation are **extremely preterm,** also referred to as **extremely low gestational age newborns (ELGANs)**; whereas infants born between 28 and 31 weeks and 6 days' gestation are **very preterm**. Moderate and late preterm infants (born between 32 and 36 week 6 days' gestation) are discussed in Chapter 119.3.

In addition to classification by gestational age, classification is also based on birthweight. **ELBW** is used to describe infants with a birthweight <1,000 g, **very low birthweight (VLBW)** describes infants 1,000-1,500 g, and **low birthweight (LBW)** describes infants <2,500 g at birth. Birthweight, in general, is a proxy for gestational age, but in the cases of intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) infants, birthweight can sometimes be misleading for true gestational age and is an additional risk factor for comorbidities of prematurity (see Chapter 119.4).

INCIDENCE

Preterm birth, or birth before 37 weeks of gestation, occurs at a rate of approximately 11% worldwide, adding up to a total of 15 million preterm births annually. Significant variations in preterm birthrates exist between countries, with an approximate rate of 10% in the United States. The U.S. preterm birthrate declined 1% in 2020 to 10.09%. Most of this decline is due to a decrease in rate of late preterm births (7.40% of all births in 2020) and in preterm births less than 34 weeks' gestation (2.70%). These results are reflected in birthweight-specific categories (Fig. 119.6). Disparities in preterm birthrates continue to exist, ranging from a high of 14.39% of babies born to non-Hispanic black mothers to a low of 8.72% of babies born to non-Hispanic Asian mothers.

ETIOLOGY

The etiology of preterm birth is multifactorial and involves complex interactions between fetal, placental, uterine, and maternal factors. In the setting of maternal or fetal conditions that prompt early delivery, as well as placental and uterine pathology, causes of preterm birth can sometimes be identified (Table 119.3). Most preterm births are *spontaneous* without an identifiable cause. AMA, maternal health conditions, history of previous preterm delivery, short interpregnancy interval, and lower socioeconomic status (SES) have all been associated with preterm birth. Racial disparities also exist and can only be partially predicted when factoring in education and income level. Large population studies have found associations between maternal genetics and epigenetics and preterm birth. Gestational duration and actual preterm birth have been noted with genetic variants in the maternal genome. Many of these genes have roles in regulation of the estrogen receptor, uterine development, maternal nutrition, or vascular reactivity.

ASSESSMENT OF GESTATIONAL AGE

Ultrasound measurement of fetal crown-rump length at 11-14 weeks' gestation remains the most accurate method of gestational age estimation. Estimates based on ultrasound at later gestation are less accurate, but may be improved with newer methods and likely superior to postnatal assessment. With insufficient prenatal care or discrepancies between birthweight and predicted gestational age at birth, it remains helpful to be able to assess infants for an estimated gestational age. With a careful physical exam, one may be able to distinguish SGA and IUGR infants

Table 119.3 Identifiable Risk Factors for Preterm Birth

FETAL
Fetal distress
Multiple gestation
Erythroblastosis
Nonimmune hydrops
Polyhydramnios
PLACENTAL
Placental dysfunction
Placenta previa
Placental abruption
UTERINE
Bicornuate uterus
Incompetent cervix (premature dilation)
MATERNAL
Previous preterm birth
Preeclampsia
Experiencing racism
Chronic medical illness (cyanotic heart disease, renal disease, thyroid disease)
Short interpregnancy interval
Infection (*Listeria monocytogenes*, group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
Obesity
Substance use disorder
Extremes of maternal age
OTHER
Premature rupture of membranes
Polyhydramnios
Iatrogenic due to factors listed above
Assisted reproductive technology
Trauma

Physical maturity

	−1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm:−1 <40 mm: −2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola–no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (–1), tightly (–2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Fig. 119.7 Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.)*

from preterm infants. Compared with a premature infant of appropriate weight, an infant with IUGR has a reduced birthweight and may appear to have a disproportionately larger head relative to body size; infants in both groups lack subcutaneous fat. Neurologic maturity (nerve conduction velocity) in the absence of asphyxia correlates with gestational age despite reduced fetal weight. Physical signs may be useful in estimating gestational age at birth. The commonly used **Ballard scoring system** is accurate to within 2 weeks of actual gestational age (Figs. 119.7-119.9).

Neuromuscular maturity

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140-180°	110-140°	90-110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Fig. 119.8 Neuromuscular criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.)*

Maturity Rating

Score	Weeks
– 10	20
– 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Fig. 119.9 Maturity rating. The physical and neurologic scores are added to calculate gestational age. *(From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. J Pediatr. 1991;119:417–423.)*

NURSERY CARE

At birth, the general measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administer vitamin K are the same for premature infants as for those of normal weight and maturity (see Chapter 123). Additional considerations are the need for (1) thermal control and monitoring of the heart rate and respiration, (2) advanced respiratory support, and (3) special attention to the details of fluid requirements and nutrition that may in turn lead to considerations of IV access. Preterm infants are at an increased risk of early and late-onset neonatal sepsis compared with their term counterparts. Routine procedures that disturb these infants may result in hypoxia and stress. The benefits of regular and active participation by the parents in the infant's care in the nursery and the question of prognosis for later growth and development require special consideration.

Thermal Control

Avoidance of hypothermia and hyperthermia decreases the risk of morbidity and mortality in ELBW and VLBW infants. Neonates in general, and ELBW and VLBW infants to an even greater extent, are at increased risk of heat loss compared with older children due to an

increased body surface/weight ratio, decreased epidermal and dermal skin thickness, minimal subcutaneous fat, and an immature nervous system.

Preterm infants should be kept in a **neutral thermal environment**. This environment comprises a set of thermal conditions, including air and radiating surface temperatures, relative humidity, and airflow, at which heat production (measured experimentally as oxygen consumption) is minimal and the infant's core temperature is within the normal range. The neutral thermal environment is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity, while minimizing heat loss through conduction, convection, radiation, and evaporation. The optimal environmental temperature for minimal heat loss and oxygen consumption for an unclothed infant is one that maintains the infant's core temperature at 36.5–37.0°C (97.7–98.6°F). The smaller and less mature the infant, the higher is the environmental temperature required. Infant warmth can be maintained by heating the air to a desired temperature or by servo-control. Continuous monitoring of the infant's temperature is required to maintain optimal body temperature. **Kangaroo care,** especially in LBW infants, with direct skin-to-skin contact between infant and parent, with a hat and blanket covering the infant, is to be encouraged (and not delayed), without untoward effects on thermoregulation.

Maintaining increased relative humidity for preterm infants in the first weeks of life aids in stabilizing body temperature by reducing heat loss at lower environmental temperatures. The ideal humidity and duration of increased humidity at a specific gestational age is not known, but typically is maintained between 60% and 80% for a week. Humidification of inspired air for infants requiring respiratory support prevents drying and irritation of the lining of respiratory passages and aids in thinning viscid secretions and reducing insensible water loss. Humidification should be gradually weaned after the first week of life to promote skin barrier formation and to reduce the risk of microbial growth associated with prolonged excessive humidity. The infant should also be weaned and then removed from the incubator or radiant warmer when the gradual change to the atmosphere of the nursery does not result in a significant change in the infant's temperature, color, activity, vital signs, or rate of weight gain.

Oxygen Administration

Administering oxygen to reduce the risk of injury from hypoxia and circulatory insufficiency (risk of cerebral palsy, death) must be balanced against the risk of hyperoxia to the eyes **(retinopathy of prematurity [ROP])** and injury to the lungs due to generation of free radicals. For ELBW infants at birth, guidelines should be followed to determine need for supplemental oxygen during resuscitation to maintain goal O_2 saturation limits (see Chapter 123).

After the initial resuscitation period, ideal target O_2 saturation limits for ELBW infants should be within the range of 90–95% for most infants.

Nutrition for the High-Risk Infant

In the absence of early parenteral and enteral nutritional support, deficits in protein, energy, and micronutrients will quickly accrue, placing the infant at risk for poor growth and neurodevelopmental outcomes. The goals of early nutritional support for extremely premature infants include approximating the rate and composition of growth for a normal fetus at the same postmenstrual age. Achieving this goal requires an understanding of the intrauterine growth rate to be targeted as well as the unique nutrient requirements of premature infants. Strategies to prevent growth failure include a combined approach of early parenteral and enteral nutrition, fortification of human milk, and the use of standardized feeding guidelines. Careful monitoring of weight gain, length, and head circumference using appropriate growth curves and timely biochemical assessment of bone health and potential nutritional deficiencies is paramount. Consultation with an experienced neonatal dietitian is important to achieve optimal outcomes.

Early Parenteral Nutrition

In the absence of IV amino acids, extremely premature infants lose 1–2% of body protein stores per day. IV amino acids and dextrose should be started immediately after birth. Many units use a *starter* or *stock* solution of amino acids and dextrose to accomplish this goal in infants weighing <1,500 g. Ideally at least 2 g/kg of amino acids should be given in the first 24 hours after birth, with a goal of at least 3 g/kg within 24-48 hours after birth. To meet total energy requirements, up to 3 g/kg of IV lipids will also be needed.

Benefits of Human Milk

Maternal milk is the preferred source of enteral nutrition for premature infants and is associated with decreased in-hospital morbidity, including lower rates of necrotizing enterocolitis (NEC), late-onset sepsis, bronchopulmonary dysplasia (BPD), and severe ROP. Maternal milk feeding is also associated with superior neurodevelopmental outcomes at 18- and 30-months corrected age compared to infants fed premature formula. Donor human milk is increasingly being used when maternal milk is not available, but it is typically lower in protein and energy content than preterm maternal milk and may result in suboptimal growth unless adequately fortified. Although donor human milk has been associated with a reduction in NEC, the impact of donor human milk on neurodevelopmental outcomes remains unclear.

Enteral Nutrition

Early enteral feedings are recommended in ELBW and VLBW infants, typically beginning between 6 and 48 hours of life with some period of trophic/minimal enteral feeding volume. Feedings are typically advanced slowly (15-30 mL/kg/day) with a target goal of delivering approximately 110-135 kcal/kg/day and 3.5-4.5 g protein/kg/day. To accomplish these goals, human milk must be fortified, or a premature formula can be given. Additional supplements such as vitamins, iron, or other micronutrients may be required and should be based on ongoing assessment and in consultation with a neonatal dietitian.

Standardized Feeding Guidelines

Standardized feeding guidelines should be developed incorporating evidence-based strategies for the provision of parenteral and enteral nutrition in ELBW and VLBW infants, including a plan to manage feeding intolerance. Regardless of the specific protocol, having a feeding guideline leads to improved outcomes (e.g., time to regain birthweight, time to reach full enteral nutrition), decreased rates of late-onset sepsis and NEC, improved growth at 36 weeks' postmenstrual age, and reduced length of hospital stay.

Transitioning to Discharge Nutrition

The earlier an infant is born before expected, the greater the likelihood that not all nutritional deficits will be resolved before hospital discharge. Regardless of weight gain during the initial hospital stay, there is strong evidence for improved bone mineralization with the use of higher concentrations of calcium and phosphorus after discharge. Fortified human milk or preterm formula with higher concentrations of protein, minerals, and trace elements is often recommended after discharge. An individualized approach to postdischarge nutrition should be developed to transition from the NICU and communicated with the outpatient pediatrician who will be caring for the infant.

Prevention of Infection

Extremely preterm infants have an increased susceptibility to infection; thus meticulous attention to infection control is required. Prevention strategies include strict compliance with handwashing and universal precautions, minimizing the risk of catheter contamination and duration, meticulous skin care, encouraging early appropriate advancement of enteral feeding, education and feedback to staff, and surveillance of nosocomial infection rates in the nursery. Although no one with an active infection should be permitted in the nursery, the risks of infection must be balanced against the disadvantages of limiting the infant's contact with the family. Early and frequent participation by parents in the nursery care of their infant does not increase the risk of infection when preventive precautions are maintained.

Preventing transmission of infection from infant to infant is difficult because often neither term nor premature newborn infants have clear clinical evidence of an infection early in their course. When epidemics occur within a nursery, cohort nursing and isolation rooms should be used. **Hand hygiene** is of upmost importance. Because premature infants have immature immune functions, some will develop nosocomial infection even when all precautions are followed.

Awareness of overutilization of antibiotics may mitigate associated complications both at the population level (cost and antibiotics resistance) and for the individual patient (alteration of the microbiome).

Routine **immunizations** should be given on the regular schedule based on chronological age at standard doses.

Transfusion Medicine

Premature infants are at increased risk of anemia due to impaired erythropoiesis and iatrogenesis due to frequent laboratory sampling. Most infants with a birthweight less than 1,000 g admitted to the NICU receive at least one blood transfusion during their stay. The need for repeated transfusion can be minimized by a thoughtful approach to laboratory sampling and establishing set hemoglobin thresholds for transfusions. A multicenter randomized controlled trial in infants 22 weeks 0 days to 28 weeks 6 days found that a lower transfusion threshold resulted in fewer transfusions per infant without an impact on neurodevelopment at 22 to 26 months' corrected gestational age. The need for transfusions depends in part on the cardiopulmonary stability of the patient, postnatal age, birthweight, and the etiology of the anemia. For severe cardiopulmonary disease, transfusions are recommended to maintain the hematocrit between 40% and 45%. For asymptomatic stable neonates with anemia of prematurity, maintaining the hematocrit at ~25% is acceptable.

Transfusion of platelets is another common practice in the NICU. Premature infants are at high risk for intraventricular hemorrhage in the first week of life, which historically prompted platelet transfusion at thresholds now considered safe. Additionally, preterm infants may also develop thrombocytopenia in the setting of severe bleeding or infection. A multicenter randomized controlled trial found that infants randomized to a higher platelet transfusion threshold ($50{,}000/m^3$) paradoxically had a higher rate of death or severe bleeding that infants randomized to a lower threshold ($25{,}000/m^3$).

IMMATURITY OF DRUG METABOLISM

Great care must be taken when prescribing and dosing medications for premature infants (Table 119.4). Renal clearance of almost all substances excreted in the urine is diminished in newborn infants, and to even a greater extent in premature infants. The glomerular filtration rate rises with increasing gestational age; therefore drug dosing recommendations vary with age. For drugs primarily excreted by the kidneys, longer intervals between dosages are often needed with increasing degree of prematurity. Drugs that are detoxified in the liver or require chemical conjugation before renal excretion should also be given with caution and in doses smaller than usual.

Many drugs apparently safe for adults on the basis of toxicity studies may be harmful to newborns, especially premature infants. Oxygen and a number of drugs have proved toxic to premature infants in amounts not harmful to term infants. Thus, administering any drug, particularly in high doses, that has not undergone pharmacologic testing in premature infants should be undertaken carefully after risks have been weighed against benefits.

Table 119.4 Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
$NaHCO_3$	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Furosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones
Heparin (*not* low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

MORBIDITY AND MORTALITY

Rates of neonatal morbidity and mortality are high in extremely preterm infants, and risks increase with decreasing gestational age and lower birthweight (Table 119.5). Data on extremely preterm infants born between 2003 and 2007 found that 42% of VLBW infants developed BPD, 12% developed ROP requiring treatment, 11% NEC, 36% late-onset sepsis, 16% grade III or IV intraventricular hemorrhage, and 3% periventricular leukomalacia (PVL). Mortality increased with lower gestational age, with a 94% mortality in infants born at 22 weeks and 8% mortality at 28 weeks. The group of extremely preterm infants had a 28% mortality rate, with 37% surviving without a significant neonatal morbidity.

Another study found that morbidity and mortality among VLBW infants decreased between 2000 and 2009. This study was limited to liveborn infants with birthweights of 500-1,500 g. For infants born in 2009, this study found a 12.4% mortality rate; 28% of infants developed BPD, 7% severe ROP, 5% NEC, 15% late-onset sepsis, 6% grade III or IV IVH, and 3% PVL; 51% survived without significant neonatal morbidity.

Outcomes are improving with time; survival among infants born at 22-24 weeks' gestation is ~50–80% in units providing active management. The percentage surviving without neurodevelopmental impairment has also increased. Factors that reduce morbidity and mortality in extremely preterm infants include higher birthweight and gestational age, receipt of antenatal corticosteroids, female sex, singleton pregnancy, and active

Table 119.5 Neonatal Morbidities Associated with Prematurity

RESPIRATORY
Respiratory distress syndrome (hyaline membrane disease)
Bronchopulmonary dysplasia*
Pneumothorax, pneumomediastinum; interstitial emphysema
Congenital pneumonia
Apnea
CARDIOVASCULAR
Patent ductus arteriosus
Hypotension
Bradycardia (with apnea)
HEMATOLOGIC
Anemia (early or late onset)
GASTROINTESTINAL
Poor gastrointestinal function—poor motility
Necrotizing enterocolitis*
Hyperbilirubinemia—indirect and direct
Spontaneous gastrointestinal isolated perforation
METABOLIC-ENDOCRINE
Hypocalcemia
Hypoglycemia
Hyperglycemia
Metabolic acidosis
Hypothermia
Euthyroid but low thyroxine status
Osteopenia
CENTRAL NERVOUS SYSTEM
Intraventricular hemorrhage*
Periventricular leukomalacia*
Seizures
Retinopathy of prematurity*
Deafness
RENAL
Hyponatremia
Hypernatremia
Hyperkalemia
Renal tubular acidosis
Renal glycosuria
Edema
OTHER
Infections* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)

*Major neonatal morbidities.

resuscitation planned at delivery. With improvement in neonatal care, a growing number of centers offer a trial of resuscitation starting at 22 0/7 weeks if that is consistent with parental goals. Outcome prediction tools such as those based on data from the United States (NICHD-VON) or UK (BAPM) and the latter organization's framework to guide management are resources for the clinician that can be used for parental counseling. The prediction tools underscore that extreme prematurity is still associated with significant risk of both mortality and major neonatal morbidities. For infants who survive to discharge, prematurity, as well as neonatal morbidities, put them at increased risk for developmental delays and impairment as they age (see Chapter 119.5). Perinatal centers should develop consensus guidelines regarding an approach to periviable birth to ensure a consistent approach to both maternal and neonatal care. Balanced and unbiased antenatal counseling that includes shared decision-making between neonatologists, obstetricians, and families is imperative.

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119.3 Moderate and Late Preterm Infants

Erik Brandsma

Whereas the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), and the WHO have precise definitions for preterm, term, and postterm births, there has been some debate on defining subcategories of preterm infants. Because outcomes vary widely within broad gestational age range groups, consensus on definitions of subcategories is important. Based on a now widely adopted recommendation from a 2005 National Institutes of Health (NIH) sponsored workshop, infants born at 34 0/7 through 36 6/7 weeks' gestation are considered late preterm. The WHO defines **moderate to late preterm** birth as infants born at 32 0/7 through 36 6/7 weeks' gestation. Therefore most define **moderate preterm** infants as those born at 32 0/7 through 33 6/7 weeks' gestation.

The initial effect of the NIH-sponsored workshop and the resulting 2007 AAP Clinical Report from the Committee on Fetus and Newborn on late preterm infants was encouraging. The report continues to be a resource for pediatricians caring for late preterm infants, listing recommended minimum criteria for their discharge. A 2019 update from the Committee on Fetus and Newborn addresses the concern of the increasing incidence of late preterm birth since 2015.

The risk of morbidity in the individual infant born moderate or late preterm is lower than infants born before 32 weeks of gestation. Because late and moderate preterm births account for approximately 75% and 11.5% of preterm births in the United States, respectively, morbidities in this group continue to be a significant burden on the healthcare system. Etiology of preterm birth is discussed elsewhere (see Chapter 117.2). The majority of moderate and late preterm births are associated with spontaneous preterm labor, preterm premature rupture of membranes (PPROM), and multiple gestation.

MODERATE PRETERM INFANT

Moderate preterm infants are at increased risk for postnatal morbidities, although to a lesser extent and severity than very preterm infants. The most common morbidities associated with preterm birth at this gestational age are temperature instability, respiratory distress, apnea, sepsis, hypoglycemia, feeding difficulties, and hyperbilirubinemia. Moderate preterm infants with birthweight >1,500 g and an unremarkable NICU course are thought to be at minimal risk for IVH and do not routinely need a head ultrasound. Similarly, the AAP does not recommend universal screening for ROP at this gestational age, unless birthweight is below 1,500 g or in select cases for infants with a history of significant cardiopulmonary compromise. Little research has examined moderate preterm infants as an isolated group; more often these infants are grouped with very preterm infants when assessing complications and outcomes. A cohort of approximately 7,000 infants born between 29 and 33 weeks' gestational age were found in a recent study to have a mean hospital stay of 33.3 days. Moderate and late preterm infants are at increased risk of mortality as well. The increased risk of mortality is modest, approximately 10-fold for moderate preterm infants and fourfold for late preterm infants compared to term infants (22 and 8.2 per 1,000 live births, respectively), but because these infants comprise close to 90% of preterm infants overall, this group as a whole contributes significantly to infant mortality.

LATE PRETERM INFANT

As described previously, the overall rate of prematurity has increased gradually since 2015. Most of the increase in overall preterm birthrate can be contributed to infants born late preterm. These infants account for approximately 7.5% of all births and almost three fourths of all preterm births in the United States. Historically, late preterm infants were referred to as *near-term infants,* and the approach to their care was similar to that of term infants. It has been increasingly recognized that late preterm infants have significantly increased morbidity, as well as mortality, compared with their term counterparts. Overall, compared to their term counterparts, late preterm infants have approximately a sevenfold risk of morbidities and fourfold risk of mortality. There is an increased incidence of congenital anomalies in preterm infants, but even when these infants are excluded, late preterm infants continue to have significantly more morbidities. Immediately after birth, there is an increased risk of requiring resuscitation, as well as increased incidence of hypoglycemia, respiratory distress due to respiratory distress syndrome (RDS) or transient tachypnea of the newborn (TTN) apnea, and

difficulty with thermoregulation. Their average birth hospital length of stay is approximately 9 days compared to 2 days for term infants. Additional concerns during this initial hospital stay include feeding difficulties and jaundice. They have a higher rehospitalization rate compared to their term peers and an increased risk of long-term morbidities and even mortality (e.g., sudden infant death syndrome [SIDS]). Some studies suggest a higher risk of lower school readiness at kindergarten and increased risk of academic difficulties in childhood when comparing late preterm infants with term peers.

In addition to universal routine newborn care, the potential morbidities associated with preterm birth need to be addressed. This starts before birth with possible interventions to prevent preterm birth or a course of betamethasone for the pregnant women at risk for preterm birth within 7 days as recommended by ACOG and continues in the delivery room, where measures should be in place to prevent and treat common preterm birth associated morbidities such as hypothermia and hypoglycemia. Whether infants are taken care of in a NICU or in a well-baby nursery, continued vigilance is required to address the potential consequences of physiologic immaturity, such as poor feeding, dehydration, and hyperbilirubinemia. Follow-up visits should occur early and additional visits may be required to ensure the infant thrives. Because of ongoing health risks that the preterm infant faces in infancy and childhood, awareness and documentation of the child's birth history is important. It is paramount that all interventions are implemented equitably, with particular attention to non-Hispanic black and Hispanic women and children, who are currently disproportionally affected by preterm birth and account for the largest increase in late preterm birth.

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119.4 Term and Postterm Infants

Andrea F. Duncan

The ACOG further divides term infants into subgroups: **early term** (37-38 6/7 weeks), **full term** (39-40 6/7 weeks), and **late term** (41-41 6/7 weeks). Many risk factors for term infants put them at higher risk for complications, such as meconium aspiration syndrome (see Chapter 129.1), hemolytic disease of the newborn (see Chapter 140), infant of a diabetic mother (see Chapter 147), and neonatal abstinence syndrome (see Chapter 145). Both SGA and large-for-gestational-age (LGA) are associated with increased morbidities.

SMALL FOR GESTATIONAL AGE AND IUGR

There is an important distinction between the terms **small for gestational age (SGA)** and **intrauterine growth restriction (IUGR)**. SGA is based on physical evaluation of an infant at birth, usually by a pediatrician or neonatologist. If the infant's weight is <10th percentile, the infant is SGA. The diagnosis of SGA does not differentiate between normal biologic growth potential and a pathologic or growth-restricted state in utero. In contrast, IUGR is a prenatal diagnosis to describe a fetus who fails to reach in utero growth potential, often diagnosed by the obstetrician using intrauterine growth curves and measures of compromise (e.g., abnormal Doppler flow measurements) (Fig. 119.10). This measure is independent of growth centile at birth. Therefore not all infants with IUGR are SGA, and, similarly, not all infants who are SGA have IUGR.

Although it is important to understand the difference between SGA and IUGR, many studies evaluate postnatal outcomes based on a diagnosis of either SGA or IUGR.

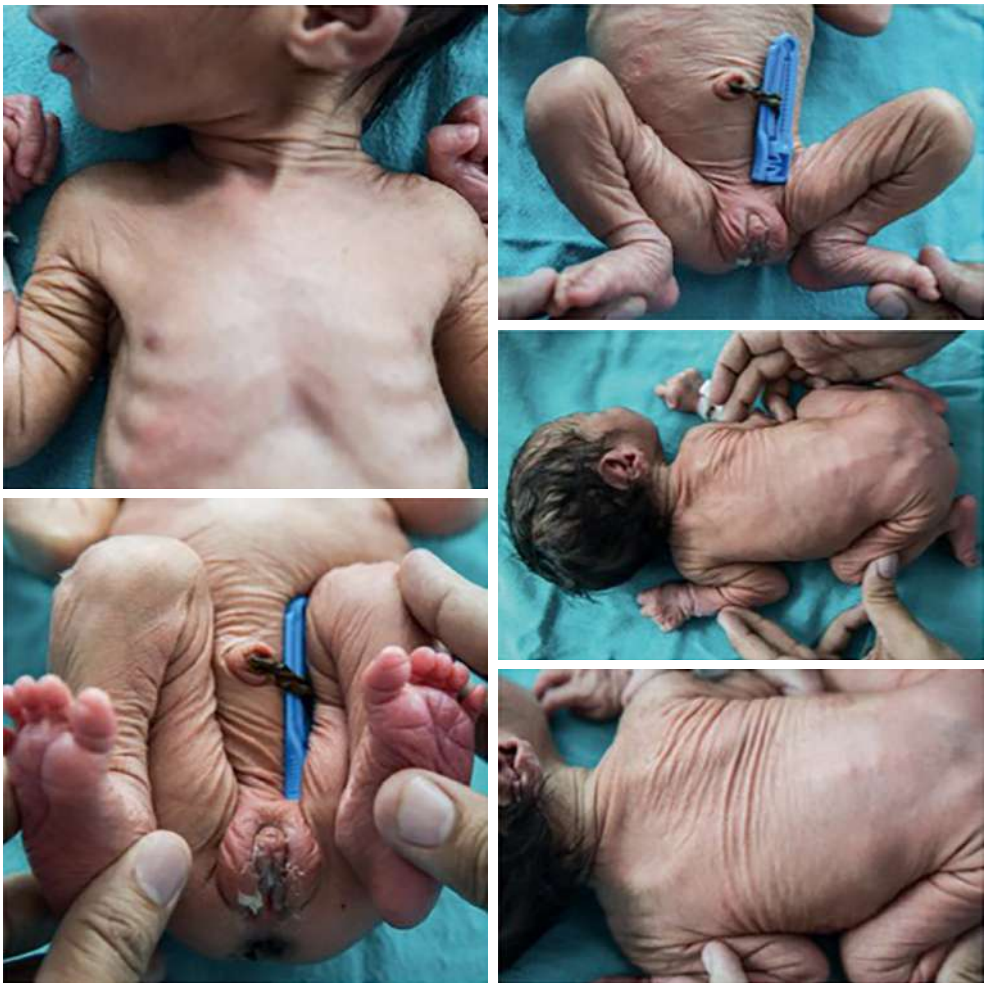

Fig. 119.10 This is a 36-week male neonate with a birthweight of 1,600 g who was born to a mother with severe preeclampsia. This baby was noted to have asymmetric intrauterine growth restriction (IUGR). Note the loss of fat over the body, visible rib cage, excessive skin folds noted over the whole body, and relatively large head compared to the body. *(From Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clin Med Insights Pediatr. 2016;10:67–83.)*

Table 119.6 Factors Often Associated with Intrauterine Growth Restriction

FETAL
Chromosomal (trisomies, microdeletions, copy number variants) and monogenetic disorders
Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis)
Congenital anomalies—syndrome complexes
Irradiation
Multiple gestation
Pancreatic hypoplasia
Insulin deficiency (production or action of insulin)
Insulin-like growth factor type I deficiency
PLACENTAL
Decreased placental weight, cellularity, or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Placental mesenchymal dysplasia
Twin transfusion syndrome
MATERNAL/PATERNAL
Preeclampsia
Hypertension or renal disease, or both
Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)
Malnutrition (micronutrient or macronutrient deficiencies)
Chronic illness
Sickle cell anemia
Drugs (opiates, alcohol, cigarettes, cocaine, prescribed medications, antimetabolites)

Table 119.7 Characteristics of Symmetric vs Asymmetric IUGR

CHARACTERISTICS	SYMMETRIC IUGR	ASYMMETRIC IUGR
Typical period of insult and presentation	Earlier gestation (often second trimester)	Later gestation (often detected in the third trimester)
Percentage of all IUGR cases	20–30%	70–80%
Etiology	Genetic disorders Congenital infections	Placental insufficiency
Antenatal scan	Proportionately decreased head circumference (HC), abdominal circumference (AC), biparietal diameter, and femur length	Only abdominal circumference decreased
Cell number	Decreased	Normal
Cell size	Normal	Decreased
Postnatal anthropometry	All parameters (HC, length, and weight) reduced	Reduced weight, HC normal, length low to normal
Features of malnutrition	Less pronounced	More pronounced

IUGR, Intrauterine growth restriction.
Adapted from Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: –part 2. *J Matern Fetal Neonatal Med.* 2016 Mar 15:1–12.

IUGR is indicative of compromise in utero and is associated with medical conditions that interfere with the circulation and efficiency of the placenta, with the development or growth of the fetus, or with the general health and nutrition of the mother (Table 119.6). Many factors are common to both prematurely born and LBW infants with IUGR. IUGR is associated with decreased insulin production or insulin-like growth factor (IGF) action at the receptor level. Infants with IGF-1 receptor defects, pancreatic hypoplasia, or transient neonatal diabetes have IUGR. Genetic mutations affecting the glucose-sensing mechanisms of the pancreatic islet cells result in decreased insulin release (loss of function of the glucose-sensing glucokinase gene) and give rise to IUGR.

IUGR may be a normal fetal response to nutritional or oxygen deprivation; therefore the issue is not the IUGR but rather the ongoing risk of fetal malnutrition or hypoxia. IUGR is often classified as *reduced growth* that is *symmetric* (head circumference, length, and weight equally affected) or *asymmetric* (with relative sparing of head growth) (Table 119.7). **Symmetric IUGR** often has an earlier onset in the first trimester of pregnancy and is associated with diseases that seriously affect fetal cell number, such as conditions with chromosomal, genetic, malformation, teratogenic, infectious, or severe maternal hypertensive etiologies. It is important to assess gestational age carefully in infants suspected to have symmetric IUGR because incorrect overestimation of gestational age may lead to the diagnosis of symmetric IUGR. It is also important to assess carefully for dysmorphic features in infants with symmetric IUGR. **Asymmetric IUGR** is often of late onset in the second half of pregnancy, demonstrates preservation of Doppler waveform velocity to the carotid vessels, and is associated with poor maternal nutrition or with late onset or exacerbation of maternal vascular disease (preeclampsia, chronic hypertension).

Table 119.8 lists common problems of infants with IUGR. In addition, in both preterm and term infants, IUGR is associated with increased risk of cardiovascular disease across the life span, and both SGA and IUGR are associated with an increased risk of neurodevelopmental impairment. To properly manage infants born IUGR and SGA, clinicians must prepare for the possible perinatal morbidities (e.g., hypoglycemia, hypothermia, pulmonary hypertension, feeding intolerance), perform any diagnostic testing needed to determine the etiology, and monitor closely for long-term deficits (e.g., growth, neurodevelopment, cardiovascular).

Table 119.8 Problems of Infants Small for Gestational Age or with Intrauterine Growth Restriction*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia-acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia-hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH†

*Other problems include pulmonary hemorrhage and those common to the gestational age–related risks of prematurity if born at <37 wk.
†TORCH, Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex infection.
↓, Decreased; ↑, increased.

LARGE-FOR-GESTATIONAL-AGE INFANTS

Infants with birthweight >90th percentile for gestational age are called **large for gestational age (LGA)**. Neonatal mortality rates decrease with increasing birthweight until approximately 4,000 g, after which they increase. These oversized infants are usually born at term, but

preterm infants with high weights for gestational age also have a significantly higher mortality than infants of the same size born at term; maternal diabetes and obesity are predisposing factors. Some infants are constitutionally large because of large parental size. LGA infants, regardless of their gestational age, have a higher incidence of shoulder dystocia and birth injuries, such as cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face. LGA infants are also at increased risk for hypoglycemia and polycythemia.

The incidence of congenital anomalies, particularly congenital heart disease, is also higher in LGA infants than in term infants of normal weight.

POSTTERM INFANTS

Postterm infants are those born after 42 weeks (294 days) of gestation, as calculated from the mother's LMP. Historically, approximately 12% of pregnancies resulted in delivery after 42 weeks. However, with current evidence demonstrating significantly increased maternal, fetal and neonatal risks after 42 weeks' gestation, obstetric interventions to induce labor often occur before 42 weeks, resulting in a decreasing rate of postterm births. The cause of true postterm birth or postmaturity is unknown, though some have been attributed to genetic influences and defects in fetal production of parturition hormones. Postterm infants are often dysmature, with normal length and head circumference but may have decreased weight, indicating impaired nutritional supply from placental insufficiency. Infants born postterm in association with presumed placental insufficiency may have various physical signs. Desquamation, long nails, abundant hair, pale skin, alert faces, and loose skin, especially around the thighs and buttocks, give them the appearance of having recently lost weight; meconium-stained nails, skin, vernix, umbilical cord, and placental membranes may also be noted. Common complications of postmaturity include perinatal depression, meconium aspiration syndrome, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia.

Perinatal mortality is 5.8% for infants born at ≥42 weeks' gestational age, compared to 0.7% for those born at term. Mortality may be due to placental insufficiency or umbilical cord compression resulting in hypoxemia and asphyxia. Mortality has been greatly reduced through improved obstetric management. Data suggest that elective delivery between the 39th and 41st week of gestation for both nulliparous and multiparous women is associated with decreased maternal and neonatal complications compared with those who were expectantly managed.

Careful obstetric monitoring, including nonstress testing (NST), biophysical profile (BPP), or Doppler velocimetry, usually provides a rational basis for choosing one of three courses: nonintervention, induction of labor, or cesarean delivery. Induction of labor or cesarean birth may be indicated in older primigravidas >2 weeks beyond term, particularly if evidence of fetal distress is present. Medical problems in the newborn are treated if they arise.

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119.5 Follow-Up of High-Risk Infants After Discharge

Andrea F. Duncan

DISCHARGE FROM THE HOSPITAL

Numerous criteria need to be met before a high-risk infant is ready for discharge from the hospital (Table 119.9). Before discharge, infants should be taking most or all nutrition by nipple, either bottle or breast. Some medically fragile infants may require discharge while receiving gavage feedings or after placement of a gastrostomy tube, after the parents have received appropriate training and education. Growth should be occurring at steady increments, with a goal weight gain of approximately 30 g/day. Temperature should be stable and normal in an open crib. Infants should have had no recent episodes of apnea or bradycardia requiring intervention for at least 5-7 days before discharge. Stable infants recovering from BPD may be discharged on a regimen of home oxygen given by nasal cannula as long as careful follow-up is arranged with home pulse oximetry monitoring and outpatient visits. Some children may require discharge on higher ventilatory support in partnership with pulmonology. All infants with birthweight <1,500 g or gestational age <30 weeks at birth should undergo an eye examination to screen for ROP. If born preterm, hemoglobin or hematocrit should be determined to evaluate for possible anemia of prematurity. Every infant should have a hearing test before discharge. Routine vaccinations should be given based on chronological age before discharge. In addition, palivizumab (Synagis) should be given to eligible infants during respiratory syncytial virus (RSV) season immediately before discharge for prophylaxis against RSV, with continued monthly doses arranged as an outpatient as appropriate.

If all major medical problems have resolved and the home setting is adequate, premature infants may then be discharged when their weight approaches 1,800-2,000 g, they are >34-35 weeks postmenstrual age (PMA), and all the above criteria are met. Parental education, close follow-up, and healthcare provider accessibility are all essential for early discharge protocols. The primary caregivers for the infant should have a chance to provide infant care in the hospital with nursing supervision and support before discharge home. All high-risk infants should follow up with their primary care provider within a few days of discharge and should

Table 119.9 Readiness for Discharge of High-Risk Infants Criteria

Resolution of acute life-threatening illnesses
Ongoing follow-up for chronic but stable problems:
Bronchopulmonary dysplasia
Intraventricular hemorrhage
Necrotizing enterocolitis after surgery or recovery
Ventricular septal defect, other cardiac lesions
Anemia
Retinopathy of prematurity
Hearing problems
Apnea
Cholestasis
Stable temperature regulation
Gain of weight with enteral feedings:
Breastfeeding
Bottle feeding
Gastric tube feeding
Free of significant apnea
Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated
Hearing screenings
Ophthalmologic examination if <30 wk of gestation or <1,500 g at birth
Parental knowledge, skill, and confidence documented in:
Administration of medications (diuretics, methylxanthines, aerosols, etc.)
Use of oxygen, apnea monitors, oximeters
Nutritional support:
Timing
Volume
Mixing concentrated formulas
Recognition of illness and deterioration
Basic cardiopulmonary resuscitation
Infant safety
Scheduling of referrals:
Primary care provider
Neonatal follow-up clinic
Occupational therapy/physical therapy
Imaging (head ultrasound)
Assessment of and solution to social risks

Data from American Academy of Pediatrics, American College of Obstetricians: *Guidelines for Perinatal Care*. 7th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2013.

Table 119.10 Sequelae of Prematurity

IMMEDIATE	LATE
Hypoxia, ischemia	Intellectual disability, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Intellectual disability, spasticity, seizures, post hemorrhagic hydrocephalus
Sensorineural injury	Hearing and visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, pulmonary hypertension, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other sequelae	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

be followed in a follow-up program that tracks medical and neurodevelopmental outcomes.

POSTDISCHARGE FOLLOW-UP

Medical Follow-Up

Even after discharge from the hospital, high-risk infants need very close medical follow-up. They continue to be at increased risk for poor weight gain and failure to thrive. In the setting of viral illness, premature infants are at increased risk for significant respiratory distress. Infants who are sent home on oxygen need very close medical follow-up with frequent visits and assessments, often with pulmonology. Table 119.10 lists common sequelae of prematurity.

Medically complex infants can go home with a multitude of subspecialty appointments to help manage existing morbidities secondary to prematurity, for example, cardiology for management of a patent ductus arteriosus or pulmonary hypertension, pulmonary for BPD, nephrology for hypertension, ophthalmology for ROP, neurosurgery for hydrocephalus, and neurology for history of seizures. The extensive follow-up requirements can be overwhelming and daunting for families. It is very important that these infants have a primary provider who serves as their "medical home" to help coordinate and assimilate the care from all these providers for families. This may be their primary care provider or subspecialty program provider.

Developmental Follow-Up

Premature infants are at much greater risk for neurodevelopmental delays than their term counterparts; the more preterm, the greater the risk of delay. In addition, certain postnatal morbidities (severe BPD, grade III or IV intraventricular hemorrhage, severe ROP, seizures) are associated with significantly increased risk of developmental delays. It is very important that these infants, particularly those born preterm, are followed and assessed for developmental delay, so that if delays are detected targeted interventions can be instituted as early as possible.

It is recommended that developmental follow-up be available for infants born <32 weeks' PMA, or at a minimum <28 weeks' PMA and/or <1 kg birthweight. Developmental follow-up in the United States is most often provided in a neonatal follow-up program for the first 2-3 years of life, and in some cases, until school age. Assessments focus on five main developmental domains: cognitive development, language development, fine and gross motor skills, social development, and emotional development. Although many assessments exist, the most widely used assessment in the United States is the *Bayley Scales of Infant and Toddler Development, 4th Edition.*

It is important to note that for at least the first 2 years of life, a child's corrected age should be used in determining whether a delay exists. Corrected age is calculated by subtracting the weeks born premature from a child's chronological age. In doing so, a corrected age accounts for a child's prematurity. There is some debate whether corrected age should continue to be used after age 2 years.

If it is determined that a delay exists, a child should be referred for appropriate therapy immediately to help minimize the delay as the child ages. Federal law under the Individuals with Disabilities Act requires states to provide *early intervention* services to children <3 years old with developmental delay. States vary greatly in how delay is defined and what services are offered. Early intervention is associated with improved cognitive outcomes in infancy and preschool age, but not lasting into school age. Motor outcomes are improved in infancy for children who receive early intervention, but this has not been shown to be a lasting effect into preschool and school age. However, these findings are difficult to interpret, given the heterogeneity of early interventions included in the reviews. With *targeted* interventions for specific delays, functional outcomes are improved.

Premature infants, especially those with a history of grade III or IV intraventricular hemorrhage or PVL seen on head imaging, are also at increased risk of motor impairments. Cerebral palsy is a *nonprogressive* but *permanent* disorder of movement and posture caused by disturbance to the developing immature brain. Historically, cerebral palsy had not been diagnosed until 18-24 months of age, but it can be diagnosed within the first 6 months of life. Early detection is critical to leveraging the neuroplasticity present in the very early years of life for improved function. International guidelines for early assessment and diagnosis of cerebral palsy and standardized assessments such as the General Movements Assessment (GMA) and the Hammersmith Infant Neurological Examination (HINE) are recommended in the guidelines to help identify children at high risk for or with cerebral palsy within the first few months to a year of life. This enables these children to access early intervention services and therapy at an earlier age, as well as undergo more frequent surveillance as needed.

Children with a history of prematurity who do not show significant developmental delays in the first few years of life are still at risk of later developing learning disabilities, attention problems, and decreased school achievement. Continued screening by their primary care provider is needed as these children age. More subtle deficits may not be recognized until school age; therefore continued surveillance is critical.

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Chapter 120

Transport of the Critically Ill Newborn

David A. Munson

REGIONALIZED CARE OF NEWBORNS

The concept of regionalized care for neonates emphasizes the importance of providing regionalized care for infants in facilities with adequate personnel and equipment for an infant's severity of illness. Ideally, pregnant people should give birth to infants at a facility with the appropriate level of expertise and resources to care for the degree of prematurity and illness of the infant. Very low birthweight (VLBW) infants, or infants <1,500 g at birth, have decreased morbidity and mortality when born at **Level III** hospitals. In a meta-analysis, neonatal or predischarge death occurred in 38% of VLBW infants receiving care at a non–Level III hospital and 23% of those receiving care at a Level III hospital. A main objective of *Healthy People 2020* addresses this issue, with a goal of increasing the proportion of VLBW infants born at Level III hospitals or subspecialty perinatal centers to 83.7%. When possible it is more preferable to transport the pregnant person to meet the goals of regionalization.

LEVELS OF NEONATAL CARE

A **Level I** facility must be able to provide *basic neonatal care*. Appropriate equipment and staff must be available to perform neonatal resuscitation and care for healthy term and late preterm infants. In addition, Level I facilities must have the capacity to work to stabilize ill or preterm infants before transport to a higher level of care. A Level I nursery is the minimum requirement for a hospital providing inpatient maternity care. Providers at Level I facilities usually include pediatricians, family physicians, and nurse practitioners.

In addition to the care provided at a Level I facility, **Level II** nurseries must also be capable of providing care to moderately ill term infants with problems expected to resolve quickly. Level II centers also care for infants born ≥32 weeks' gestational age and >1,500 g at birth; therefore they must be comfortable with treating conditions common in this population, such as difficulty with oral feeds, apnea of prematurity, respiratory distress requiring continuous positive airway pressure (CPAP), and temperature regulation. These centers must also be capable of stabilizing infants born <32 weeks' gestation and <1,500 g until transfer to a higher-level facility is feasible, including the ability to intubate and provide mechanical ventilation for a brief duration if necessary. In addition to providers in Level I facilities, Level II facilities also typically have pediatric hospitalists, neonatologists, and neonatal nurse practitioners.

Level III NICUs are equipped to care for extremely preterm and critically ill neonates in addition to those infants cared for at Level I and II units. Level III units must have continuously available personnel and equipment to treat conditions commonly seen in this population, such as respiratory distress syndrome, pulmonary hypertension, and need for total parenteral nutrition. Resources should be available to obtain and interpret urgent imaging needed (e.g., CT, echocardiography). Pediatric subspecialists and pediatric surgeons should be available either on-site or through prearranged consultative agreements.

In addition to the care available at Level III neonatal intensive care units (NICUs), **Level IV** NICUs are also capable of providing continuously available pediatric subspecialty consultation and pediatric surgical intervention. Many Level IV sites are located at regional children's hospitals and also serve to provide outreach education. Level IV NICUs also have the capacity to provide extracorporeal membrane oxygenation (ECMO), an intervention that requires surgeons for catheter placement and ECMO specialists who are typically nurses or respiratory therapists with additional training in managing the ECMO circuit.

TRANSPORT OF THE CRITICALLY ILL NEONATE

In the event that a neonate requires a higher level of care, transport must be arranged to a unit with the appropriate level of care available. Additional decisions that need to be made before transport include composition of the transport team, equipment required for transport, and mode of transportation.

The composition of the **transport team** varies depending on personnel available and the needs of the infant being transported. The transport team often comprises at least two individuals, whether two registered transport trained nurses (RNs), an RN and a respiratory therapist, or an RN and a paramedic. In addition, a neonatologist, neonatology fellow, or neonatal nurse practitioner will sometimes accompany the transport team for critically ill neonates. A **medical command physician** is also available and can communicate with the transport team during the transport, as needed. The command physician is also able to communicate with the referring neonatologist to discuss the case and offer advice while the transport team is en route.

Transport staff must be competent in the treatment of common neonatal conditions and complications, as well as neonatal procedures. Many Level IV facilities have specialized teams designed only for neonatal transports. However, a Cochrane review found no evidence to support or to refute improved infant morbidity or mortality when transport occurred with a specialized neonatal team versus those that transported both neonatal as well as pediatric patients. Depending on the volume of neonatal transports and composition of the team, staff may have limited exposure to neonatal transports and procedures. **Simulation-based learning** is recommended by the American Academy of Pediatrics (AAP) Section on Transport Medicine (SOTM) as a method to help achieve and retain competency in rarely experienced procedures, as well as improve team interactions for transport teams.

The **transport vehicle** should be equipped with appropriate medicines, intravenous (IV) fluids, oxygen tanks, catheters, chest tubes, endotracheal tubes (ETTs), laryngoscopes, bag-valve-mask, and infant warming device. It should be well illuminated and have ample room for emergency procedures and monitoring equipment. Additional needs for an individual transport should be anticipated. Specifically, inhaled nitric oxide is not standard equipment for most transport teams and will need to be requested if thought necessary for safe transport. For neonates with hypoxemic ischemic encephalopathy who require hypothermia therapy, a servo-controlled cooling device is recommended as it will achieve the target temperature faster and there is less risk of overshooting the goal temperature. Prostaglandin E1 should be available for suspected ductal dependent congenital heart disease.

Common **modes of transport** include ground transport by ambulance and air transport by helicopter or fixed-wing aircraft. The stability of the infant, travel distance, traffic, and weather must all be taken into account when deciding the most appropriate mode of transportation.

Steps should be taken to stabilize the infant, as able, in a timely fashion before the transport. Securing an airway, providing oxygen, assisting with infant ventilation, providing antimicrobial therapy, maintaining the circulation, providing a warmed environment, checking a glucose level, and placing IV or arterial lines or chest tubes should be initiated, if indicated, before transport. Appropriate placement of lines and ETT should be evaluated before transport.

Some hospitals and their associated level IV NICUs offer transport of a patient on ECMO. Most commonly this is designed to transport a patient who is already cannulated onto ECMO who needs subspecialized care such as evaluation for transplant, or assessment for longer-term mechanical cardiac support. In other situations, a hospital may have the capacity to cannulate a patient onto ECMO, but do not have a program in place to support the patient for the coming days. These patients may therefore include more common patients who require ECMO such as neonates with persistent pulmonary hypertension, severe hypoxemic respiratory failure, sepsis, congenital diaphragmatic hernia, or hypoplastic left heart syndrome. In these circumstances, a transport team needs to include an ECMO specialist or perfusionist, and commonly adds a

critical care physician or surgeon. There are some programs that will bring the necessary personnel and equipment to cannulate a patient onto an ECMO circuit at the referring hospital before transport. There are considerable logistical challenges and added risks for transporting a patient on ECMO. These include inadvertent decannulation, problems with sustaining flow on the circuit, and bleeding.

Risks of transport and **consent** for transportation should be reviewed and obtained from parents before transport. Although transport teams attempt to anticipate and prepare for possible complications that could occur during transport, there is an inherent risk of complications, including death, in the event of a decompensation during transport resulting from the limited resources and personnel available. It is intrinsically more difficult to perform procedures in the physically confined space of an ambulance or helicopter. Additionally, there is the risk associated with the mode of transport itself including car and helicopter crashes. Parents should be made aware of these risks. Efforts should be made to allow parents to see their baby briefly before transport.

Communication with the transport team as well as the receiving facility is paramount throughout the transport process. Available prenatal history, information on the infant's resuscitation and hospital course, laboratory data, and radiographic images should be sent with the transport team to the receiving hospital to aid in future care. Video-assisted telecommunications can assist in giving the **medical command physician** visual as well as audio information about what is happening on-site before the patient is loaded onto the ambulance.

Reverse transport of an infant back to a lower level of care should be considered when infants are stabilized or have received and recovered from their subspecialist or surgical interventions, and no longer require the higher-level care available at the receiving hospital. Transport back to the hospital of birth aids in appropriate utilization of resources, decreases costs of care, and may further promote parent–infant bonding because of proximity to the mother's home.

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Chapter 121

Clinical Manifestations of Diseases in the Newborn Period

Kathleen A. Gibbs and Eric C. Eichenwald

A variety of conditions that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders can be caused by prematurity, congenital malformations, disruption of chromosome structure, or acquired diseases and injuries.

ABNORMAL MOVEMENTS

Neonatal seizures usually suggest a central nervous system (CNS) disorder, such as hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage, stroke, cerebral anomaly, subdural effusion, or meningitis (see Chapter 633.7). In the neonate, seizures can also be secondary to hypocalcemia, hypoglycemia, benign familial seizures, or rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal.

Seizures in premature infants are often subtle and associated with abnormal eye movement (fluttering, tonic horizontal deviation, sustained eye opening with ocular fixation) or facial movement (chewing, tongue thrusting); the motor component is often that of tonic extension of the limbs, neck, and trunk. Autonomic phenomena include hypertension and tachycardia. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have subtler manifestations of seizure activity. **Apnea** may be the first manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to seizures outside the neonatal period. Electroencephalographic (EEG) evidence of seizures can occur without clinical manifestations, particularly in preterm infants. If seizures are suspected, video-EEG monitoring will improve the detection of both subtle and electrographic but clinically silent seizures. Seizures contribute to brain injury and the impact of treatment on neurodevelopmental outcomes is an active area of research, particularly in patients with HIE. Although many medications used to treat seizures have side effects, it is recommended to treat both clinical and subclinical seizures.

Seizures should be distinguished from the **jitteriness**, defined as *recurrent tremors,* that may be present in healthy newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic neonates. An examiner can suppress the tremors by holding the infant's extremity; jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures.

After severe birth asphyxia, infants may exhibit **motor automatisms** characterized by recurrent oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized EEG discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Failure to move an extremity **(pseudoparalysis)** suggests fracture, dislocation, or a paralytic brachial plexus injury, often following a traumatic delivery. It is also seen in neonatal stroke (paralytic) as well as septic arthritis, osteomyelitis, and other infections that cause pain on movement of the affected part.

ABNORMAL TONE

Hypotonia, or low tone in one or more extremities, may be due to specific genetic etiologies or as a result of pathology in the peripheral or central nervous system. Features in the history and physical examination can help narrow the differential diagnosis and guide further diagnostic evaluations (see Chapter 647). A history of decreased fetal movement in utero may be suggestive of a congenital myopathy, or spinal muscular atrophy. In a male infant with cryptorchidism, Prader-Willi syndrome can be considered. **Hypotonia** is a common finding in an infant with trisomy 21. Hypertonia is less common and should be distinguished from fixed joint contractures seen in arthrogryposis. If present in the hours after birth and associated with the need for resuscitation after birth, a case of HIE should be considered.

ALTERED MENTAL STATUS

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, an inborn error of metabolism (IEM), or, almost any severe disease. Shortly after birth, lethargy is most likely caused by maternal medications (opioids, magnesium, general anesthesia) or moderate to severe HIE. Lethargy appearing after the second day should suggest infection or an IEM manifesting with hyperammonemia, acidosis, or hypoglycemia. Lethargy with emesis may suggest increased intracranial pressure or an IEM.

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Irritability may be a sign of discomfort accompanying intraabdominal conditions, meningeal irritation, drug withdrawal, infections, trauma (birth or nonaccidental), or any condition producing pain. It must be distinguished from normal crying behavior associated with hunger or benign environmental stimuli.

The lack of an interest to feed may indicate a sick infant and should prompt a careful search for infection, a CNS (brain or spine) or peripheral nervous system disorder, IEM, or intestinal obstruction.

APNEA

Periods of apnea, particularly in premature infants, can be attributed to many different underlying causes (see Chapter 125). When apnea occurs in a term infant, it should be considered pathologic until proven otherwise, and an immediate diagnostic evaluation for the underlying cause is imperative.

CONGENITAL ANOMALIES

Congenital anomalies are a common cause of neonatal morbidity and mortality worldwide (see Chapters 98–100). Early recognition of anomalies during fetal life is important to plan for delivery room management and subsequent neonatal care. Some malformations, including congenital heart disease, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, and intestinal obstruction, require immediate medical/surgical therapy for postnatal survival (Table 121.1). Prenatal and postnatal testing strategies, including advanced imaging techniques and genetic testing, have improved the specific diagnosis of congenital anomalies (see Chapter 103.1). Historically, genetic testing was performed by obtaining a karyotype with or without *fluorescence in situ hybridization* (FISH). A karyotype can identify a large number of chromosomal abnormalities; FISH can test for classic microdeletion syndromes such as 22q11. Chromosomal microarray is also indicated for genetic testing of infants with congenital anomalies because it can identify microdeletions or microduplications that are too small to be detected by more traditional techniques. In cases where a common aneuploidy, such as trisomy 13, 18, or 21, is suspected, obtaining a conventional karyotype and/or FISH may be the more appropriate test as those results are available in a few days. Whole exome sequencing (WES) uses next-generation sequencing to identify variants in protein coding genes that may be responsible for a disease phenotype. Rapid WES can have results available in 1-2 weeks. This can be used in a critically ill infant with a suspected genetic disorder that lacks a unifying diagnosis, and it may lead to a specific treatment and prognosis. Limitations of both microarray and WES include the identification of variants that may not be pathogenic in nature. Parents should receive genetic counseling as part of any testing strategy. It is important that healthcare providers are aware of the indication and limitations of the type of genetic test being performed.

CYANOSIS

Central cyanosis generates a broad differential diagnosis encompassing respiratory, cardiac, CNS, infectious, hematologic, and metabolic etiologies (Table 121.2). Typically, 5 g/dL of deoxyhemoglobin must be present in the blood for central cyanosis to be clinically apparent. If respiratory insufficiency is caused by pulmonary conditions, respirations tend to be rapid with increased work of breathing. If caused by CNS depression, respirations tend to be irregular and weak and are often slow. Cyanosis unaccompanied by obvious signs of respiratory difficulty suggests cyanotic congenital heart disease or methemoglobinemia. Cyanosis resulting from congenital heart disease may be difficult to distinguish clinically from cyanosis caused by respiratory disease. Episodes of cyanosis may also be the initial sign of hypoglycemia, bacteremia, meningitis, shock, or pulmonary hypertension. **Peripheral acrocyanosis** is common in neonates and thought to represent peripheral venous congestion associated with immature control of peripheral vascular tone. It does not usually warrant concern unless poor perfusion is suspected.

GASTROINTESTINAL DISTURBANCES

Vomiting during the first day of life can suggest obstruction in the upper digestive tract, metabolic disease, or may be physiologic**. Abdominal distention** with emesis**,** usually a sign of intestinal obstruction or an intraabdominal mass, may also be seen in infants with enteritis, necrotizing enterocolitis (NEC), isolated intestinal perforation, ileus accompanying sepsis, respiratory distress, ascites, or hypokalemia. Imaging studies are indicated when obstruction is suspected; proximal intestinal obstruction often occurs with a normal physical examination, whereas distal obstruction will likely be accompanied by distention. Vomiting may also be a nonspecific symptom of an illness such as sepsis with associated abdominal distention and ileus. It is a common manifestation of overfeeding, as well as gastroesophageal or physiologic reflux. Rarely, vomiting is caused by pyloric stenosis, milk protein allergy, duodenal ulcer, stress ulcer, an IEM (hyperammonemia, metabolic acidosis), or adrenal insufficiency. Vomitus containing blood is usually a sign of a serious illness, but the benign possibility of swallowed maternal blood associated with the delivery process should also be considered. Tests for maternal vs fetal hemoglobin can help

Table 121.1 Common Life-Threatening Congenital Anomalies

ANOMALY	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room; nasogastric tube cannot be passed through nares Suspect CHARGE (coloboma of eye, heart anomaly, choanal atresia, retardation, genital and ear anomalies) syndrome
Pierre Robin syndrome, Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation; nasogastric tube cannot be placed in stomach Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia) syndrome
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, or cocaine use
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephaly, meningomyelocele	Polyhydramnios, elevated α-fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

Table 121.2 Differential Diagnosis of Cyanosis in the Newborn

CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION
Birth asphyxia
Intracranial hypertension, hemorrhage
Oversedation (direct or through maternal route)
Diaphragm palsy
Neuromuscular diseases
Seizures

RESPIRATORY DISEASE
Airway
Choanal atresia/stenosis
Pierre Robin syndrome
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)

Lung
Respiratory distress syndrome
Transient tachypnea
Meconium aspiration
Pneumonia (sepsis)
Pneumothorax
Congenital diaphragmatic hernia
Pulmonary hypoplasia

CARDIAC RIGHT-TO-LEFT SHUNT
Abnormal Connections (Pulmonary Blood Flow Normal or Increased)
Transposition of great vessels
Total anomalous pulmonary venous return
Truncus arteriosus
Hypoplastic left heart syndrome
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis

OBSTRUCTED PULMONARY BLOOD FLOW (PULMONARY BLOOD FLOW DECREASED)
Pulmonic atresia with intact ventricular septum
Tetralogy of Fallot
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect
Tricuspid atresia
Single ventricle with pulmonic stenosis
Ebstein malformation of tricuspid valve
Persistent fetal circulation (persistent pulmonary hypertension of newborn)

METHEMOGLOBINEMIA
Congenital (hemoglobin M, methemoglobin reductase deficiency)
Acquired (nitrates, nitrites)

INADEQUATE DELIVERY
Inadequate ambient O2 or less O2 delivered than expected (rare)
Disconnection of O2 supply to nasal cannula, head hood
Connection of air, rather than O2, to a mechanical ventilator

SPURIOUS/ARTIFACTUAL
Oximeter artifact (poor contact between probe and skin, poor pulse searching)
Arterial blood gas artifact (contamination with venous blood)

OTHER
Hypoglycemia
Adrenogenital syndrome
Polycythemia
Blood loss

From Smith F: Cyanosis. In: Kliegman RM: *Practical Strategies in Pediatric Diagnosis and Therapy*. Philadelphia: Saunders; 1996.

discriminate between these possibilities. Bilious emesis in a term infant should be considered a surgical emergency with a presumed diagnosis of intestinal malrotation with or without volvulus until proven otherwise. This finding warrants urgent contrast radiography of the upper gastrointestinal tract (see Chapter 376.3).

Diarrhea may be a symptom of overfeeding (especially high–caloric density formula), acute gastroenteritis, congenital diarrhea syndromes, or malabsorption, or it may be a nonspecific symptom of infection. Diarrhea should be differentiated from the normal loose, seedy, yellow stool seen typically in breastfed infants. Diarrhea may occur in conditions accompanied by compromised circulation of part of the intestinal or genital tract, such as mesenteric thrombosis, NEC, strangulated hernia, intussusception, and torsion of the ovary or testis.

HYPOTENSION

Hypotension in term infants implies hypovolemic shock (hemorrhage, dehydration), a systemic inflammatory response syndrome (bacterial sepsis, intrauterine infection, NEC, cardiac dysfunction, myocarditis, asphyxia-induced myocardial stunning, anomalous coronary artery), congenital heart disease with ductal-dependent systemic blood flow (hypoplastic left heart syndrome, congenital aortic stenosis), pneumothorax, pneumopericardium, pericardial effusion, or metabolic disorders (hypoglycemia, adrenal insufficiency).

Hypotension is a common problem in sick preterm infants and may also be caused by any of the problems noted in a term infant. Some extremely low gestational age infants do not respond to fluids or inotropic agents but may improve with administration of intravenous hydrocortisone (Fig. 121.1). Sudden onset of hypotension in a very low birthweight (VLBW) infant suggests pneumothorax, intraventricular hemorrhage, or subcapsular hepatic hematoma. Strategies used to support blood pressure include volume expansion with crystalloid and/or colloid, vasopressors (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin), or corticosteroids (hydrocortisone) (see Chapter 85).

JAUNDICE

Jaundice during the first 24 hours of life warrants diagnostic evaluation and should be considered pathologic until proven otherwise. Hemolytic disease of the newborn due to rhesus blood group system (Rh) isoimmunization or blood type compatibility are the most common cause (see Chapter 140). Intrauterine infections (e.g., syphilis, cytomegalovirus, and toxoplasmosis), early-onset sepsis, or gestational alloimmune liver disease (formerly described as neonatal hemochromatosis) should be considered in infants with neonatal cholestasis, identified by an increase in *direct* bilirubin value. Immediate evaluation includes obtaining total and direct bilirubin, infant blood type and Coombs status, CBC, and reticulocyte count. There are nomograms specific to the age (in hours) of the infant to guide the initiation of therapeutic interventions depending on the levels of serum bilirubin values (see Chapter 137). Phototherapy is the standard first-line therapy. In the case of Coombs-positive hemolysis, strong consideration should be made to giving intravenous immunoglobulin (IVIG) if there is no response to intensive phototherapy. Double volume exchange transfusion is recommended in situations with rapidly rising indirect bilirubin levels, particularly in infants whose bilirubin levels rise over 20 mg/dL. In these cases, obtaining a serum albumin is also recommended.

Jaundice that is identified after the first 24 hours of age may be physiologic or pathologic. Physiologic conditions include breast-milk and breast-feeding jaundice. Pathologic conditions include bacterial sepsis, congenital hypothyroidism, galactosemia, congenital atresia of the bile ducts, or other conditions (see Chapter 137).

PAIN

Pain in neonates may be unrecognized and/or undertreated. The intensive care of neonates may involve several painful procedures, including blood sampling (heelstick, venous or arterial puncture), endotracheal intubation and suctioning, mechanical ventilation, and insertion of chest tubes and intravascular catheters. Pain in neonates results in

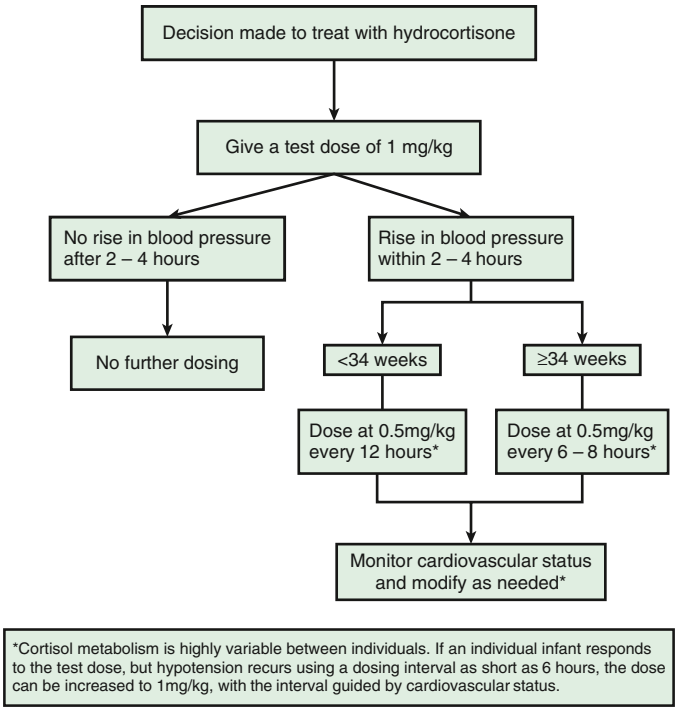

Fig. 121.1 Suggested treatment algorithm for hydrocortisone dosing in the newborn. *(From Watterberg KL. Hydrocortisone dosing for hypotension in newborn infants: less is more. J Pediatr. 2016;174:23–26.)*

obvious distress and acute physiologic stress responses, which may have developmental implications for pain in later life.

Pain and discomfort are potentially avoidable problems during the treatment of sick infants. The most common painful stimuli for healthy newborns include circumcision and phlebotomy while obtaining metabolic screening tests. There are pharmacologic and nonpharmacologic options to both prevent and treat pain. **Oral sucrose solutions** are well tolerated by most infants and have proven efficacy for procedural pain. A dorsal penile nerve block is effective to prevent procedural-related pain during a circumcision. For neonatal intensive care unit (NICU) infants, the most frequently used drugs are intermittent or continuous doses of opioids. Although the specific long-term effects of opioids and sedatives are not well established, the first concern should be the treatment and/or prevention of acute pain (Table 121.3).

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121.1 Hyperthermia

Kathleen A. Gibbs and Eric C. Eichenwald

Serious infection (pneumonia, bacteremia, meningitis, and viral infections, particularly herpes simplex or enteroviruses) may cause **fever** and must be considered, although such infections often occur without provoking a febrile response in newborn infants (see Chapter 220). Providers should consider evaluation for bacterial infection in infants <28 days old with a rectal temperature ≥38°C (100.5°F), including blood culture, urine culture, and lumbar puncture (LP), although stepwise approaches to identify low-risk patients and limiting LP to a subset of higher-risk infants are gaining favor. Fever immediately after birth may be caused by radiant warmers, maternal fever, or maternal epidural analgesia. Fever may also be caused by elevated environmental temperatures because of weather, overheated nurseries, incubators, or radiant warmers, or excessive clothing. It has also been attributed to dehydration, although *dehydration fever* is a diagnosis of exclusion in newborn infants.

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Table 121.3 Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Data from American Academy of Pediatrics Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery; Canadian Paediatric Society, Fetus and Newborn Committee. Prevention and Management of Pain and Stress in the Neonate: An Update. *Pediatrics* 2016;137:e20154271.

121.2 Hypothermia and Cold Stress

Kathleen A. Gibbs and Eric C. Eichenwald

Unexplained **hypothermia** may accompany infection or other serious disturbances of the circulation or CNS. A sudden servo-controlled increase in incubator ambient temperature to maintain body temperature is a sign of temperature instability and may be associated with sepsis or any of the conditions already mentioned.

Cold stress can lead to profound decompensation, including apnea, bradycardia, respiratory distress, hypoglycemia, and poor feeding. For this reason, it is paramount for the neonate to maintain normothermia in the delivery room and afterward, especially low birthweight and premature infants. For VLBW infants, a combination of occlusive plastic wrap, radiant warmers, and thermal mattresses to maintain normothermia can be used to reduce cold stress.

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121.3 Edema

Kathleen A. Gibbs and Eric C. Eichenwald

Generalized edema noted in the delivery room can be caused by hydrops fetalis secondary to several underlying causes (see Chapter 143). An infant with suspected hydrops in utero should be delivered at a specialty perinatal center with capacity for neonatal intubation, thoracentesis, paracentesis, and pericardiocentesis in the delivery room. If noted after 24 hours of age, causes are similar to those of older children and may be multifactorial and likely related to the underlying disease state. Edema may be due to interstitial fluid "third-spacing" due to a systemic inflammatory response seen in sepsis or NEC; or, in the immediate postoperative period, hypoalbuminemia may be due to low production in hepatic synthetic dysfunction or increased losses in underlying renal disease such a congenital nephrotic syndrome (see Chapter 567.3).

121.4 Hypocalcemia

Kathleen A. Gibbs and Eric C. Eichenwald

Hypocalcemia in a neonate can manifest as irritability, jitteriness, clonus, or seizures. Electrocardiography can show a prolonged QT interval. The cause may simply represent an exaggerated physiologic decrease in serum calcium levels within the first 24 hours of life or pathologic conditions such as genetic disorders (22q deletions), prematurity, growth restriction, perinatal hypoxia, hypomagnesemia, or maternal diabetes. Hypocalcemia is more common in term infants receiving formula than in those exclusively receiving breast milk. Most infants remain asymptomatic and can be managed conservatively with early nutrition and close monitoring, whereas symptomatic neonates should receive intravenous or oral calcium replacement.

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121.5 Hypermagnesemia

Kathleen A. Gibbs and Eric C. Eichenwald

Hypermagnesemia is most often caused by maternal administration of magnesium in the perinatal period for treatment of conditions such as preeclampsia and preterm labor, and as prophylaxis to mitigate brain injury associated with preterm birth. Infants are usually present with signs at birth and improve over the next 24-48 hours. Symptoms include respiratory depression, hypotonia, lethargy, and feeding intolerance. No treatment is indicated other than supportive measures.

Chapter 122
Nervous System Disorders

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Central nervous system (CNS) disorders are important causes of neonatal mortality and both short-term and long-term morbidity. The CNS can be injured as a result of asphyxia, hemorrhage, trauma, infection, hypoglycemia, or direct cytotoxicity. The etiology of CNS injury is often multifactorial and includes perinatal complications, postnatal hemodynamic instability, and developmental abnormalities that may be genetic and/or environmental. Predisposing factors for brain injury include chronic and acute maternal illness resulting in uteroplacental dysfunction, intrauterine infection, macrosomia/dystocia, malpresentation, prematurity, and intrauterine growth restriction. Acute and often unavoidable emergencies during the delivery process may result in mechanical and hypoxic-ischemic brain injury.

122.1 The Cranium

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Erythema, abrasions, ecchymoses, and subcutaneous fat necrosis of facial or scalp soft tissues may be noted after a normal delivery or after forceps or vacuum-assisted deliveries. The location depends on the area of contact with the pelvic bones or application of the forceps. Traumatic hemorrhage may involve any layer of the scalp as well as intracranial contents (Fig. 122.1).

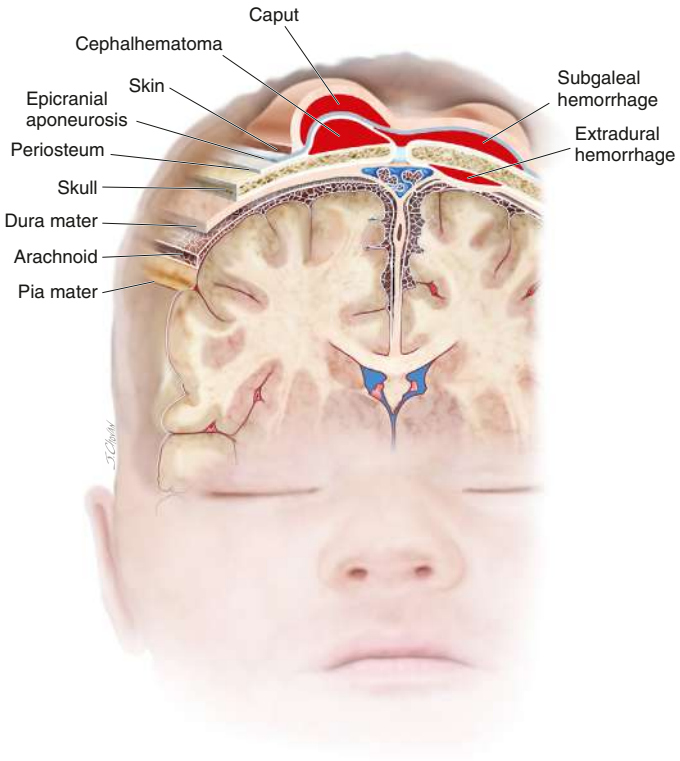

Fig. 122.1 Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. *(From Volpe JJ. Injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In: Volpe JJ, Inder TE, Darras BT, et al., eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 36-1.)*

Caput succedaneum is a diffuse, sometimes ecchymotic, edematous swelling of the soft tissues of the scalp due to the increased pressure of the vaginal and uterine walls on the fetal head during labor. The pressure causes a serosanguinous/edematous infiltration above the periosteum and below the skin or subcutaneous tissue. The edema is soft and extends across the midline of the skull, crossing suture lines and disappears within the first few days of life. Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded; they disappear during the first few weeks of life. Rarely, a hemorrhagic caput may result in shock and require blood transfusion. Analogous swelling, discoloration, and distortion of the face are seen in face presentations. No specific treatment is needed, but if extensive ecchymoses are present, hyperbilirubinemia may develop.

Cephalohematoma is a unilateral subperiosteal hemorrhage that does not cross the suture lines as it usually occurs within a single cranial plate (Fig. 122.2). Cephalohematomas occur in 1–2% of live births regardless of the mode of delivery. No discoloration of the overlying scalp occurs, and due to slow bleeding, the clinical presentation of swelling is delayed for several hours to days. The lesion becomes a firm, tense mass with a palpable rim localized over one area of the skull. Most cephalohematomas are resorbed within 3 to 4 weeks, depending on their size. They may begin to calcify by the end of the second week of life. A few remain for years as bony protuberances and are detectable on radiographs as widening of the diploic space; cystlike defects that may persist for months or years. An underlying skull fracture, usually linear and not depressed, may be associated with 10–25% of cases. A sensation of central depression suggesting but not indicative of an underlying fracture or bony defect is usually encountered on palpation of the organized rim of a cephalohematoma. Osteomyelitis of the skull is a rare complication of cephalohematoma; *Escherichia coli* and *Staphylococcus aureus* are common agents. Cephalohematomas

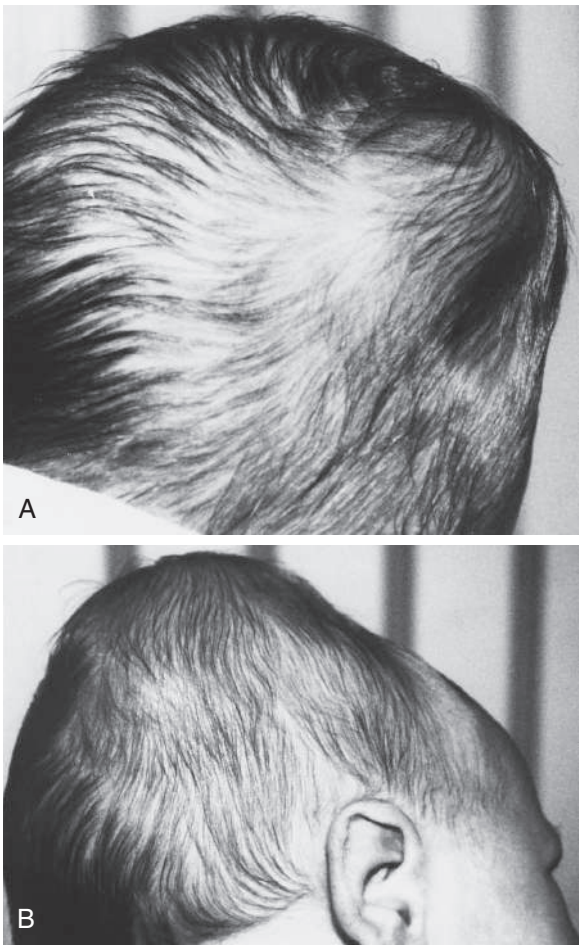

Fig. 122.2 Parietal cephalhematoma. Clinical appearance of 10-day-old infant delivered with the aid of mid-forceps. **A,** Posterior view. **B,** Right lateral view. Note prominent swelling that extends medially to the sagittal suture, posteriorly to the lambdoid suture, and laterally to the squamosal suture. *(From Volpe JJ. Injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In: Volpe JJ, Inder TE, Darras BT, et al. eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 36-3.)*

require no treatment, although phototherapy may be necessary to treat hyperbilirubinemia.

A **subgaleal hemorrhage** is a collection of blood in the loose connective tissue of the subgaleal space, located between the epicranial aponeurosis and the periosteum (see Fig. 122.1). There is often an association with vacuum-assisted delivery. A subgaleal hemorrhage manifests as a fluctuant mass that straddles cranial sutures or fontanels that increases in size after birth. The mechanism of injury is most likely secondary to rupture of emissary veins connecting the dural sinuses within the skull and the superficial veins of the scalp. Subgaleal hemorrhages are sometimes associated with skull fractures, suture diastasis, and fragmentation of the superior margin of the parietal bone. Extensive subgaleal bleeding can result in sequestration of more than 40% of the newborn's blood volume, which can potentially result in hemorrhagic shock. The mortality can be up to 14% due to hemorrhagic shock and is occasionally secondary to a hereditary coagulopathy **(hemophilia)**. In some cases, patients can develop a consumptive coagulopathy from massive blood loss. Subgaleal hemorrhages can present clinically with the triad of tachycardia, decreased hematocrit, and increasing occipital frontal circumference. When subgaleal hemorrhage is suspected, hemoglobin measurements should be performed as soon as possible and should be monitored every 4 to 8 hours, as should coagulation studies. Although it is not necessary to make the clinical diagnosis, optimal imaging for subgaleal hemorrhage is by CT or MRI. Radiographs of the skull can be done to identity accompanying fractures. These lesions typically resolve over 2 to 3 weeks.

Fractures of the skull may be caused by pressure in the setting of a forceps delivery, but they can occur rarely in uncomplicated vaginal deliveries. *Linear fractures,* the most common, cause no symptoms and require no treatment. Linear fractures should be followed up to demonstrate healing and to detect the possible complication of a leptomeningeal cyst. *Depressed fractures* often are referred to as "ping-pong" fractures because on x-ray they resemble an indented ping-pong ball. Affected infants may be asymptomatic unless they have associated intracranial injury. Surgical management of such an injury may not be necessary due to the infants' relatively thin and flexible skull bones rendering them amenable to remodeling, and intervention could be reserved for larger areas of depression. When intervention is required, the obstetric vacuum extractor is an ideal tool because it provides patent tubing unlikely to collapse during the application of suction. No traction is needed during the suction procedure, and the elevation of the depression can be ascertained by direct visualization, an audible "click" sound or a "give" sensation accompanied by an instantaneous pressure release. There is no clear recommendation for imaging in this population, but with newer techniques of low-dose CT imaging, current technology allows axial imaging to be constructed in the coronal and sagittal planes and into three-dimensional reformats, thus increasing the likelihood of detecting a fracture.

Subconjunctival and **retinal hemorrhages** are frequent; petechiae of the skin of the head and neck are also common. All are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that these hemorrhages are temporary and the result of normal events of delivery. The lesions resolve rapidly within the first 2 weeks of life.

122.2 Neonatal Traumatic Head Injuries

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Neonatal traumatic head injuries are estimated to affect ~3% of pregnancies and represent approximately 2% of neonatal deaths. Infrequently, these injuries occur during normal birth but the incidence rises in cases when the fetal head is large in proportion to the size of the mother's pelvic outlet, with prolonged labor, in breech or precipitous deliveries, or as a result of mechanical assistance with delivery. Massive **subdural hemorrhage**, often associated with tears in the tentorium cerebelli or less frequently in the falx cerebri, is rare, but is encountered more often in full-term than in premature infants. Patients with massive hemorrhage caused by tears of the tentorium or falx cerebri rapidly deteriorate and may die soon after birth. Most subdural and epidural hemorrhages resolve without intervention. Consultation with a neurosurgeon is recommended. Asymptomatic subdural hemorrhage may be noted within 48 hours of birth after vaginal or cesarean delivery. These are typically small hemorrhages, especially common in the posterior fossa, discovered incidentally in term infants imaged in the neonatal period, and usually of no clinical significance. The diagnosis of large subdural hemorrhage may be delayed until the chronic subdural fluid volume expands and produces macrocephaly, frontal bossing, a bulging fontanel, anemia, and sometimes seizures. CT scan and MRI are useful imaging techniques to confirm these diagnoses. Symptomatic subdural hemorrhage in term infants can be treated by a neurosurgical evacuation of the subdural fluid collection by a needle placed through the lateral margin of the anterior fontanel, or in severe cases an operative burr hole or craniotomy. In addition to birth trauma, **child abuse** must be suspected in all infants with subdural effusion after the immediate neonatal period. Most asymptomatic subdural hemorrhages following labor should resolve by 4 weeks of age.

Subarachnoid hemorrhage is often clinically silent in the neonate. Anastomoses between the penetrating leptomeningeal arteries or the

bridging veins are the most likely source of the bleeding. Most affected infants have no clinical symptoms, but the subarachnoid hemorrhage may be detected because of an elevated number of red blood cells in a lumbar puncture sample. Some infants experience short, benign seizures, which tend to occur on the second day of life. Rarely, an infant has a catastrophic hemorrhage and dies. There are usually no neurologic abnormalities during the acute episode or on follow-up. Significant neurologic findings should suggest an arteriovenous malformation, which can best be detected on CT or MRI.

122.3 Intracranial-Intraventricular Hemorrhage and Periventricular Leukomalacia

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Intracranial hemorrhage in preterm infants usually develops spontaneously. Less frequently, it may be caused by trauma or asphyxia, and rarely, it occurs from a primary hemorrhagic disturbance or congenital cerebrovascular anomaly. The very low birthweight infant (VLBW; birthweight <1,500 g) is at high risk for intracranial hemorrhages, with the risk for severe hemorrhage inversely related to gestational age. Intracranial hemorrhage often involves the ventricles **(intraventricular hemorrhage [IVH])** of premature infants delivered spontaneously without apparent trauma. Primary hemorrhagic disturbances and vascular malformations are rare and usually give rise to subarachnoid or intracerebral hemorrhage. In utero hemorrhage associated with maternal idiopathic or, more often, fetal alloimmune thrombocytopenia may appear as severe cerebral hemorrhage or as a porencephalic cyst after resolution of a fetal cortical hemorrhage. Intracranial bleeding may be associated with disseminated intravascular coagulation, isoimmune thrombocytopenia, and neonatal vitamin K deficiency, especially in infants born to mothers receiving phenobarbital or phenytoin.

Periventricular leukomalacia (PVL) is a disorder of the periventricular cerebral white matter that may be cystic or diffuse in nature. PVL may initially be observed during the first week of life in the VLBW infant as increased echogenicity of the periventricular white matter, sometime described as an echogenic "blush" or "flare." These areas of white matter abnormalities may become cystic on ultrasonography within 2 to 5 weeks and/or lead to ventriculomegaly from white matter volume loss, which can be visible on repeat ultrasonography at term equivalent age. Clinical risk factors for PVL include gestational age at birth and prenatal/postnatal factors including inflammation, hypoxia, postnatal steroid exposure, and metabolic disturbances.

EPIDEMIOLOGY

The overall incidence of IVH has decreased over the last few decades as a result of improved perinatal care, increased use of antenatal corticosteroids, surfactant to treat respiratory distress syndrome (RDS), and improved positive pressure mechanical ventilation strategies. The global incidence of IVH among preterm infants ranges from 14.7–44.7% with considerable variation across gestational age groups, neonatal intensive care units (NICUs), and countries. The risk for severe IVH is associated with infants with a gestational age ≤30 weeks' gestation, with the highest risk in infants born at ≤24 weeks' gestation. Infants born at >30 weeks' gestation have a low risk of severe IVH unless they have additional clinical risk factors such as low Apgar scores, metabolic acidosis, hypotension, or lack of antenatal steroids.

PVL can be described in three major pathologic forms: macroscopic cystic white matter injury, microscopic cystic white matter injury, and nonnecrotic diffuse white matter injury. Macroscopic cystic white matter injury represents the most severe form of PVL and fortunately affects <5% of very preterm infants born <32 weeks. With advances in neonatal care, there has been a shift from large cystic injury to small punctate injury. In microscopic cystic white matter injury, the necrotic areas are small and result in focal areas of gliosis, which ultrasonography is not sensitive enough to detect. The most common form of PVL in the preterm population is nonnecrotic diffuse PVL. Diffuse PVL is estimated to affect nearly a third of infants born <32 weeks and is best recognized on MRI.

PATHOGENESIS

The major neuropathologic lesions associated with VLBW infants are IVH and PVL. IVH in premature infants occurs in the gelatinous subependymal **germinal matrix**. This periventricular area is the site of origin for embryonal neurons and fetal glial cells, which migrate outwardly to the cortex. Immature and fragile blood vessels in this highly vascular region of the developing brain combined with disturbances in cerebral blood flow and coagulation predispose premature infants to hemorrhage. The germinal matrix involutes as the infant approaches 34 to 36 weeks' gestation, and the tissue's vascular integrity improves; therefore IVH is much less common in the late preterm and term infant. The cerebellum also contains a germinal matrix and is susceptible to hemorrhagic injury. **Periventricular hemorrhagic infarction (PVHI)**, previously known as **grade IV IVH**, often develops after a large IVH because of venous congestion. PVHI is not an extension of the IVH into the parenchyma. Predisposing factors for IVH include prematurity, RDS, hypoxia-ischemia, exaggerated fluctuations in cerebral blood flow (hypotensive injury, hypervolemia, hypertension), reperfusion injury of damaged vessels, reduced vascular integrity, increased venous pressure (pneumothorax, venous thrombus), or thrombocytopenia.

The pathogenesis of PVL appears to involve both intrauterine and postnatal events. A complex interaction exists between the development of the cerebral vasculature and the regulation of cerebral blood flow (both of which depend on gestational age), disturbances in the oligodendrocyte precursors required for myelination, and maternal/fetal infection and inflammation. Postnatal hypoxia or hypotension, necrotizing enterocolitis (NEC) with its resultant inflammation, and severe neonatal infection may all result in white matter injury. The risk for PVL increases in infants with severe IVH or ventriculomegaly.

CLINICAL MANIFESTATIONS

Most infants with IVH, including some with moderate to severe hemorrhages, have no initial clinical signs **(silent IVH)**. Some premature infants with severe IVH may have an acute deterioration on the second or third day of life **(catastrophic IVH)**. Hypotension, apnea, pallor, stupor or coma, seizures, decreased muscle tone, metabolic acidosis, shock, and decreased hematocrit (or failure of hematocrit to increase after transfusion) may be the first clinical indications. A *saltatory progression* may occur over several hours to days and manifest as intermittent or progressive alterations of levels of consciousness, abnormalities of tone and movement, respiratory signs, and eventually other features of the acute catastrophic IVH. Rarely, IVH may manifest at birth or even prenatally; the majority of cases of IVH in the preterm infant occur within the first 3 days of life. Of those, approximately 50% of hemorrhages occur within the first 5 hours, 70% occur within the first day of life, and by 7 days of life 95% of IVH will have occurred. A small percentage of infants have late hemorrhage, between days 14 and 30. IVH as a primary event is rare after the first month of life.

The severity of hemorrhage is defined by the location and degree of bleeding and ventricular dilation on cranial imaging. In a **grade I** hemorrhage, bleeding is isolated to the subependymal area. In **grade II** hemorrhage, there is bleeding within the ventricle *without* evidence of ventricular dilation. **Grade III** hemorrhage is IVH with ventricular dilation. In **PVHI** hemorrhage (formerly called **grade IV**, see previously), there is intraventricular and parenchymal hemorrhage (Fig. 122.3). Another grading system describes three levels of increasing severity of IVH detected on ultrasound: In **grade I,** bleeding is confined to the germinal matrix–subependymal region or to <10% of the ventricle (approximately 35% of IVH cases); **grade II** is defined as intraventricular bleeding with 10–50% filling of the ventricle (40% of IVH cases); and in **grade III**, >50% of the ventricle is involved, with dilated ventricles (see Fig. 122.3).

One of the major complications resulting from IVH is the development of **posthemorrhagic ventricular dilation (PHVD)**. Following a large IVH, multiple small clots throughout the ventricular system may obstruct

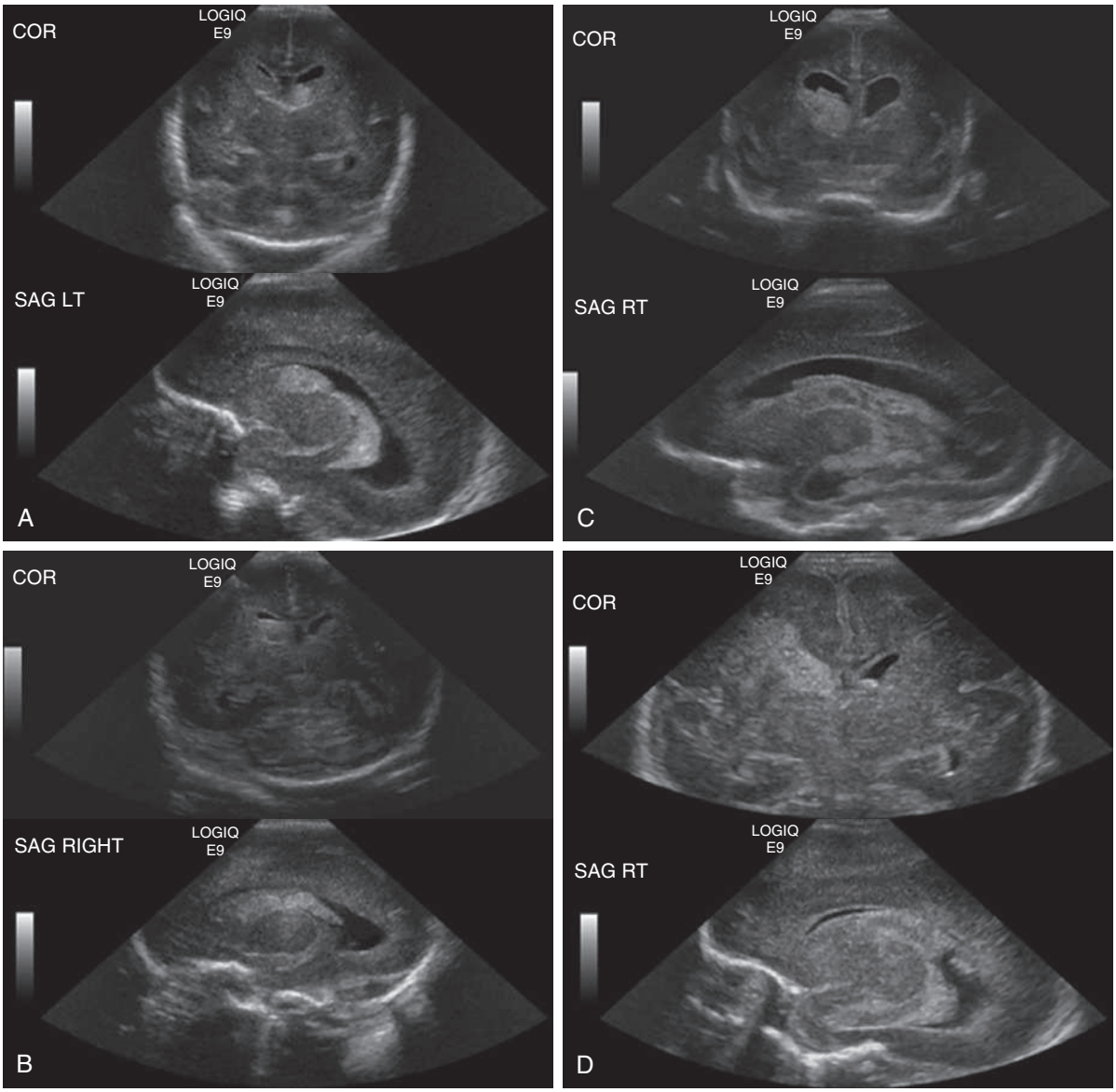

Fig. 122.3 Grading of the severity of germinal matrix–intraventricular hemorrhage (IVH): coronal (COR) and parasagittal (SAG) ultrasound scans. **A,** Germinal matrix hemorrhage, grade I. **B,** IVH (filling <50% of ventricular area), grade II. **C,** IVH with ventricular dilatation, grade III. **D,** Large IVH with associated parenchymal echogenicity (hemorrhagic infarct), grade IV. Note that the terminology has now changed for "grade IV" to periventricular hemorrhagic infarction (PVHI). (*From Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, et al., eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 24-2.*)

cerebrospinal fluid (CSF) flow and resorption, all in the face of ongoing production of CSF in the choroid plexus in the lateral ventricles and the roof of the third ventricle. The progressive accumulation of CSF changes the shape of the lateral ventricles from a slit to a balloon. The expanding ventricles distort the developing brain and intracerebral pressure (ICP) eventually starts to rise. As the preterm skull is very compliant, the ventricles can expand without pressure rising initially but eventually can result in increased ICP. PHVD develops in 30–50% of infants with severe IVH and is initially asymptomatic in most patients. *Therefore sequential cranial ultrasonography facilitates early detection*. The term ventriculomegaly is occasionally used for both infants with ventricular enlargement following IVH as well as those without hemorrhage. In infants without IVH, ventricular enlargement is more likely due to *white matter loss* rather than an accumulation of CSF. Therefore it is preferable to use the term PHVD when ventricular enlargement follows IVH.

PVL is usually clinically asymptomatic until the neurologic sequelae of white matter damage become apparent in later infancy as spasticity and/or motor deficits. PVL may be present at birth but usually occurs later, when the echodense phase is seen on ultrasound (3 to 10 days of life), followed by the typical echolucent/cystic phase (14 to 20 days).

DIAGNOSIS

Intracranial hemorrhage is suspected on the basis of history, clinical manifestations, and knowledge of the birthweight-specific risks for IVH. Associated clinical signs of IVH are typically nonspecific or absent. Neuroimaging recommendations that premature infants ≤30 weeks of gestation and selected infants with gestational age >30 weeks who are believed to be at increased risk for brain injury on the basis of identified risk factors should be screened for IVH with cranial ultrasonography. Standard ultrasonography screening includes views from the anterior and mastoid fontanelles. Additional posterior fontanelle and vascular imaging can be performed for additional information. Routine cranial ultrasonographic screening is recommended by 7 to 10 days of age, but earlier imaging may be warranted if clinical signs and symptoms are suggestive of significant injury. Repeat cranial ultrasonography screening is recommended to be performed at 4 to 6 weeks of age and at term equivalent age or before hospital discharge. CT is not considered a part of routine imaging techniques of the preterm brain. MRI for infants born ≤30 weeks gestational age is not indicated as a routine procedure, although could be offered to families of high-risk infants after a conversation about the limits of prognosticating long-term outcomes using MRI.

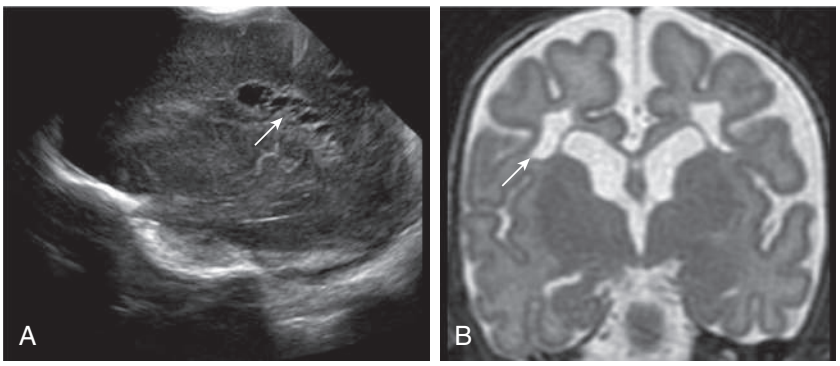

Fig. 122.4 Severe cystic periventricular leukomalacia. **A,** Parasagittal ultrasound image showing numerous large cysts superolateral to the lateral ventricle *(arrow).* **B,** Coronal T2 weighted MR image in which cysts are present superolateral to the lateral ventricles *(arrow).* (*From Neil JJ, Volpe JJ. Encephalopathy of prematurity: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. Volpe's Neurology of the Newborn. 6th ed. Philadelphia: Elsevier; 2018: Fig. 16-1.*)

Table 122.1 Short-Term Outcome of Germinal Matrix–Intraventricular Hemorrhage as a Function of Severity of Hemorrhage and Birthweight*

	DEATHS IN FIRST 14 DAYS		PVD (SURVIVORS >14 DAYS)	
SEVERITY OF HEMORRHAGE	**<750 g (n = 75)**	**751-1500 g (n = 173)**	**<750 g (n = 56)**	**751-1500 g (n = 165)**
Grade I	3/24 (12)	0/80 (0)	1/21 (5)	3/80 (4)
Grade II	5/21 (24)	1/44 (2)	1/16 (6)	6/43 (14)
Grade III	6/19 (32)	2/26 (8)	10/13 (77)	18/24 (75)
Grade III and apparent PVHI	5/11 (45)	5/23 (22)	5/6 (83)	12/18 (66)

*Values are n (%). Deaths occurring later in the neonatal period are not shown; the total mortality rates (early and late deaths) are approximately 50–100% greater for each grade of hemorrhage and birthweight than those shown in the table for early deaths alone.
PVHI, Periventricular hemorrhagic infarction; PVD, progressive ventricular dilation.
Adapted from Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn.* 6th ed. Philadelphia: Elsevier; 2018. Table 24-15; with data from Murphy BP, Inder TE, Rooks V, Taylor GA, et al. Posthemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. *Arch Dis Child Fetal Neonatal Ed.* 2002;87:F37–F41.

Table 122.2 Long-Term Outcome: Neurologic Sequelae in Survivors with Germinal Matrix–Intraventricular Hemorrhage as a Function of Severity of Hemorrhage*

SEVERITY OF HEMORRHAGE	INCIDENCE OF DEFINITE NEUROLOGIC SEQUELAE† (%)
Grade I	15
Grade II	25
Grade III	50
Grade III and apparent PVHI	75

*Data are derived from reports published since 2002 and include personal published and unpublished cases. Mean values (to nearest 5%) and considerable variability among studies was apparent, especially for the severe lesions.
†Definite neurologic sequelae included principally cerebral palsy or mental retardation, or both.
PVHI, Periventricular hemorrhagic infarction.
Adapted From Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, et al. eds. *Volpe's Neurology of the Newborn.* 6th ed. Philadelphia: Elsevier; 2018: Table 24-16.

Sequential ultrasonography appears to have the best yield for identifying lesions associated with cerebral palsy. In one study, 29% of low birthweight (LBW) infants who later experienced cerebral palsy *did not* have radiographic evidence of PVL until after 28 days of age. Ultrasound also detects the precystic and cystic symmetric lesions of PVL and the asymmetric intraparenchymal echogenic lesions of cortical hemorrhagic infarction (Fig. 122.4). Cranial ultrasonography may be useful in monitoring delayed development of cortical atrophy, porencephaly, and the severity, progression, or regression of posthemorrhagic hydrocephalus (PHH).

PHH of prematurity is a common form of pediatric hydrocephalus, accounting for 20% of shunted hydrocephalus in the United States. Under normal conditions, CSF is primarily secreted into the cerebral ventricles by the choroid plexus and moves via bulk flow through the ventricular system and subarachnoid space before being absorbed at the arachnoid villi/granulations, which are fully developed after 35 weeks. An increase in CSF production or reduction in CSF absorption may result in ventricular enlargement if the system cannot compensate for the changes. Secondary white matter injury resulting from ventricular dilation is likely exacerbated by compression and ischemia from increased ICP of symptomatic PHH. Orbitofrontal head circumference, fontanel fullness, and the splaying of sutures all show limited reliability; therefore serial neuroimaging is highly valuable for clinical decision-making for neurosurgical intervention.

PROGNOSIS

The degree of IVH and presence of PVL are strongly linked to survival and neurodevelopmental impairment (Tables 122.1 and 122.2). For infants with birthweight <1,000 g, the incidence of severe neurologic impairment (defined as Bayley Scales of Infant Development IV mental developmental index <70, psychomotor development index <70, cerebral palsy, blindness, or deafness) after IVH is highest with grade IV hemorrhage and lower birthweight. PVL, cystic PVL, and progressive hydrocephalus requiring shunt insertion are each independently associated with a poorer prognosis (Table 122.3). The risk of a poor neurodevelopmental outcome is significantly higher when severe IVH is complicated with PHVD (40–60%) and more so for infants who eventually develop PHH (75–88%). In the pre-surfactant era, up to 82% of infants with PHH who survived developed significant neurologic impairments with cerebral palsy being the most common clinical sequelae (74%). The Drainage, Irrigation, Fibrinolytic Therapy (DRIFT) trial performed neurocognitive assessments at both 2 years and 10 years after birth and demonstrated improved cognitive ability when considering birthweight, IVH grade, and sex. Infants who received DRIFT were almost twice as likely to survive without severe cognitive disability than those who received standard treatment. The

Table 122.3 Ultrasound Diagnosis of Periventricular Leukomalacia

US APPEARANCE	TEMPORAL FEATURES	NEUROPATHOLOGIC CORRELATION
Echogenic foci, bilateral, posterior > anterior	First week	Necrosis with congestion and/or hemorrhage (size >1 cm)
Echolucent foci ("cysts")	1-3 weeks	Cyst formation secondary to tissue dissolution (size >3 mm)
Ventricular enlargement, often with disappearance of "cysts"	≥2-3 months	Deficient myelin formation; gliosis, often with collapse of cyst

From Neil JJ, Volpe JJ. Encephalopathy of prematurity: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn*. 6th ed. Philadelphia: Elsevier; 2018: Table 16-6.

Table 122.4 Proposed Risk Stratification and Management of Infants with PHVD

Green Zone	Yellow Zone	Red Zone
Key criteria: Ventricular size with the following • VI ≤97th percentile and • AHW ≤6 mm And Absence of the following clinical criteria: • HC growth >2 cm per week • Separated sutures • Bulging fontanelles **Management:** • Observation in NICU • cUS twice a week until stable for 2 weeks then every 1-2 weeks until 34 weeks PMA • MRI at term equivalent	**Key criteria:** Ventricular size with the following • VI >97th percentile and • AHW >6 mm and/or TOD >25 mm And Absence of the following clinical criteria: • HC growth >2 cm per week • Separated sutures • Bulging fontanelles **Management:** • Referral to a regional center for neurosurgical review • Consider LP 2-3 times • cUS 2-3X a week until stable for 2 weeks then every 1-2 weeks until 34 weeks PMA • Neurosurgical intervention when no stabilization occurs • MRI at term equivalent	**Key criteria:** Ventricular size with the following • VI >97th percentile + 4mm and • AHW >10 mm and/or TOD >25 mm Or Any of the following clinical criteria: • HC growth >2 cm per week • Separated sutures • Bulging fontanelles **Management:** • Consider LP 2-3 times • Neurosurgical intervention including either temporizing measures or VP shunt • MRI at term equivalent

Consider alterations in NIRS (i.e., decrease cerebral oxygenation) or Doppler US (i.e., increase in Resistive Index) as additional information that may suggest impairment in cerebral perfusion and more urgent need for intervention.

VI, ventricular index; AHW, anterior horn width; cUS, cranial ultrasound; TOD, thalamo-occipital distance; LP, lumbar puncture; HC, head circumference; NIRS, near-infrared spectroscopy; NICU, neonatal intensive care unit; PMA, postmenstrual age.
From El-Dib M, Limbrick DD, Inder T, et al. Management of post-hemorrhagic ventricular dilation in the infant born preterm. *J Pediatr*. 2020;226:16–26. Fig. 5.

Early versus Late Ventricular Intervention Study (ELVIS) trial demonstrated the effectiveness of intervention at a low threshold of ventricular dilation on the outcomes of death and severe neurodevelopmental disability in preterm infants with PHVD. Post hoc analysis of this study demonstrated that infants who went on to having a shunt had better neurodevelopmental outcome scores if interventions were done at a lower threshold.

TREATMENT

No treatment is available for **IVH** once it has occurred, and the management is largely symptomatic. Seizures should be treated with anticonvulsant drugs. Anemia and coagulopathy require transfusion with packed red blood cells or fresh-frozen plasma. Shock and acidosis are treated with fluid resuscitation.

Insertion of a **ventriculoperitoneal shunt** is the preferred method to treat progressive and symptomatic **PHH**. Some infants require temporary CSF diversion before a permanent shunt can be safety inserted. Diuretics and acetazolamide are not effective. Ventricular access devices (reservoirs) and externalized ventricular drains are potential temporizing interventions, although there is an associated risk of infection and *puncture porencephaly* from injury to the surrounding parenchyma. A **ventriculosubgaleal shunt** inserted from the ventricle into a surgically created subgaleal pocket provides a closed system for constant ventricular decompression without these additional risk factors. Decompression is regulated by the pressure gradient between the ventricle and the subgaleal pocket.

One approach to therapeutic interventions is based on the severity of ultrasonographic dimensions of ventricular size (Table 122.4 and Fig. 122.5)

PREVENTION

Improved perinatal care is imperative to minimize traumatic brain injury and decrease the risk of preterm delivery. The incidence of traumatic intracranial hemorrhage may be reduced by judicious management of cephalopelvic disproportion and operative delivery. Fetal or neonatal hemorrhage caused by maternal idiopathic thrombocytopenic purpura or alloimmune thrombocytopenia may be reduced by maternal treatment with corticosteroids, intravenous immunoglobulin (IVIG), fetal platelet transfusion, or cesarean birth. Meticulous care of the VLBW infant's respiratory status and fluid-electrolyte

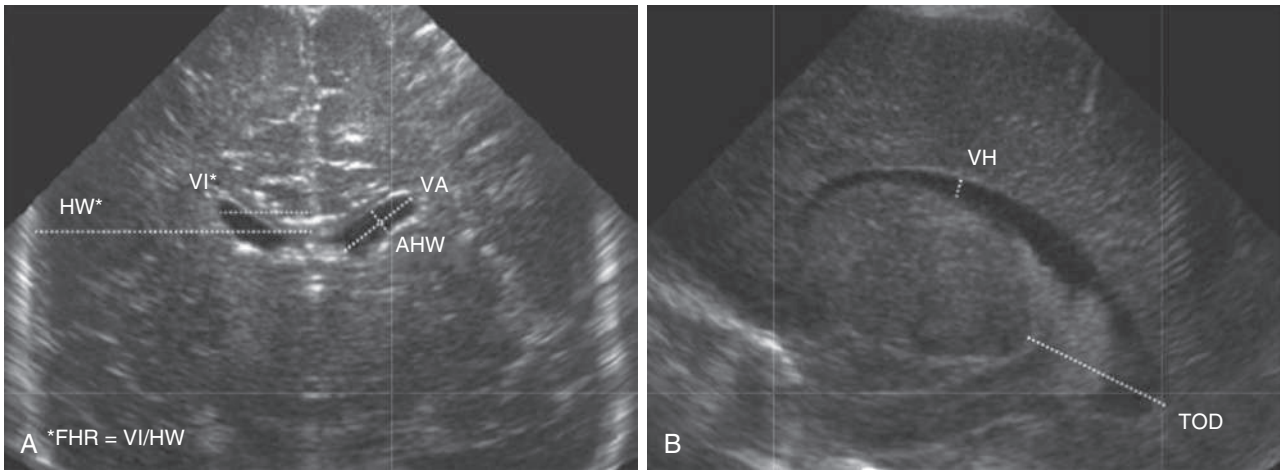

Fig. 122.5 Ventricular parameters measured in the (A) coronal and (B) sagittal planes by cranial ultrasonography. AHW, anterior horn width; FHR, frontal horn ratio; HW, hemispheric width; TOD, thalamo-occipital distance; VA, ventricular axis; VH, ventricular height; VI, ventricular index. (*From Brouwer MJ, de Vries LS, Pistorius L, et al. Ultrasound measurements of the lateral ventricles in neonates: why, how, and when? A systematic review. Acta Paediatr. 2010;99:1298–306.*)

management—avoidance of acidosis, hypocarbia, hypoxia, hypotension, wide fluctuations in neonatal blood pressure or P_{CO_2} (and secondarily fluctuation in cerebral perfusion pressure), and pneumothorax—are important factors that may affect the risk for development of IVH and PVL.

The most important protective factor against the development of IVH is antenatal administration of corticosteroids. A single course of antenatal corticosteroids is recommended for pregnant people between 24 0/7 weeks and 36 6/7 weeks of gestation who are at risk for preterm delivery within 7 days. It also may be considered for pregnant people starting at 23 weeks of gestion who are at risk for preterm delivery within 7 days, based on the family's decision regarding resuscitation. A rescue course of corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Antenatal administration of magnesium sulfate was not associated with a reduction in the incidence of IVH, although it has been associated with a reduction in the risk of cerebral palsy. Prophylactic indomethacin showed a significant reduction in the incidence of severe IVH; however, this reduction in severe IVH was not associated with a reduction in severe neurosensory impairment.

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122.4 Hypoxic-Ischemic Encephalopathy

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

Hypoxemia, a decreased arterial concentration of oxygen, frequently results in **hypoxia**, or decreased oxygenation to cells or organs. **Ischemia** refers to blood flow to cells or organs that is inadequate to maintain physiologic function. **Hypoxic-ischemic encephalopathy (HIE)** is a leading cause of neonatal brain injury, morbidity, and mortality globally. In the developed world, incidence is estimated at 1-8 per 1,000 live births, and in the developing world, estimates are as high as 26 per 1,000.

Approximately 20–30% of infants with HIE (depending on the severity) die in the neonatal period, and 33–50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, decreased intelligence quotient [IQ], learning/cognitive impairment). The greatest risk of adverse outcome is seen in infants with severe fetal acidosis (pH <6.7) (90% death/impairment) and a base deficit >25 mmol/L (72% mortality). Multiorgan failure and insult can occur (Table 122.5).

ETIOLOGY

Neonatal encephalopathy and seizures, in the absence of major congenital malformations or metabolic or genetic syndromes, appear to be caused by perinatal events. Brain MRI or autopsy findings in full-term neonates with encephalopathy demonstrate that 80% have acute injuries, <1% have prenatal injuries, and 3% have non–hypoxic-ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from maternal infections, exposures, diabetes, toxemia or postmaturity.

Table 122.5 Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECTS
Central nervous	Hypoxic-ischemic encephalopathy, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integumentary	Subcutaneous fat necrosis
Hematologic	Disseminated intravascular coagulation

Table 122.6 Topography of Brain Injury in Term Infants with Hypoxic-Ischemic Encephalopathy and Clinical Correlates

AREA OF INJURY	LOCATION OF INJURY	CLINICAL CORRELATES	LONG-TERM SEQUELAE
Selective neuronal necrosis	Entire neuraxis, deep cortical area, brainstem and pontosubicular	• Stupor or coma • Seizures • Hypotonia • Oculomotor abnormalities • Suck/swallow abnormalities	• Cognitive delay • Cerebral palsy • Dystonia • Seizure disorder • Ataxia • Bulbar and pseudobulbar palsy
Parasagittal injury	Cortex and subcortical white matter Parasagittal regions, especially posterior	• Proximal-limb weakness • Upper extremities affected > lower extremities	• Spastic quadriparesis • Cognitive delay • Visual and auditory processing difficulty
Focal ischemic necrosis	Cortex and subcortical white matter Vascular injury (usually middle cerebral artery distribution)	• Unilateral findings • Seizures common and typically focal	• Hemiparesis • Seizures • Cognitive delays
Periventricular injury	Injury to motor tracts, especially lower extremity	• Bilateral and symmetric weakness in lower extremities • More common in preterm infants	• Spastic diplegia

Adapted from Volpe JJ, ed. *Neurology of the Newborn*. 4th ed. Philadelphia: Saunders; 2001.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (see Chapter 117). Uterine contractions may further reduce umbilical oxygenation, depressing the fetal cardiovascular system and CNS and resulting in low Apgar scores and respiratory depression at birth.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) severe anemia (severe hemorrhage, hemolytic disease); (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage; or (4) failure to breathe after birth because of in utero CNS injury or drug-induced suppression.

PATHOPHYSIOLOGY AND PATHOLOGY

The topography of cerebral injury typically correlates with areas of decreased cerebral blood flow and areas of relatively higher metabolic demand, although regional vulnerabilities are impacted by gestational age and severity of insult (Table 122.6). After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generates increased amounts of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamatergic mechanism has a role in neurotoxicity. Whether this mechanism involves tissue accumulation of an abnormal amount of glutamate or altered sensitivity to the interaction between glutamate and its endogenous family of receptors (i.e., *N*-methyl-D-aspartate [NMDA], amino-3-hydroxy-5-methyl-4-isoxazole propionate [AMPA], and kainite) is unknown. However, receptor activation results in a cascade of events that leads to cell death by swelling (oncosis) or apoptosis. Along with these changes in the CNS, there are also potentially exacerbating bioenergetic changes as a result of the circulatory response with increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, at first trying to maintain perfusion of the brain, heart, and adrenal glands in preference to the lungs, liver, kidneys, and intestine.

The pathology of hypoxia-ischemia in tissues outside the CNS depends on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (see Chapter 130). If fetal distress produces gasping, amniotic fluid contents (i.e., meconium, desquamation products, lanugo) may be aspirated into the trachea or lungs with subsequent complications, including pulmonary hypertension and pneumothoraces.

Table 122.7 Poor Predictive Variables for Death/Disability After Hypoxic-Ischemic Encephalopathy

- Low (0-3) 10 min Apgar score
- Need for CPR in the delivery room
- Delayed onset (≥20 min) of spontaneous breathing
- Severe neurologic signs (coma, hypotonia, hypertonia)
- Seizures onset ≤12 hr or difficult to treat
- Severe, prolonged (~7 days) EEG findings including burst suppression pattern
- Prominent MRI basal ganglia/thalamic lesions
- Oliguria/anuria >24 hr
- Abnormal neurologic exam ≥14 days

CPR, Cardiopulmonary resuscitation; EEG, electroencephalogram.

CLINICAL MANIFESTATIONS

At delivery, the presence of meconium-stained amniotic fluid indicates that fetal distress may have occurred. At birth, affected infants may have neurologic impairment and may fail to breathe spontaneously. Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also nonspecific initial signs of potential HIE. During the ensuing hours, infants may be hypotonic, may change from a hypotonic to a hypertonic state, or their tone may appear normal (Tables 122.7 and 122.8). Cerebral edema may develop during the next 24 hours and result in profound brainstem depression. During this time, seizure activity may occur; seizures may be severe and refractory to standard doses of anticonvulsants. Although most often a result of the HIE, seizures in asphyxiated newborns may also be caused by vascular events (hemorrhage, arterial ischemic stroke, or sinus venous thrombosis), metabolic derangements (hypocalcemia, hypoglycemia), CNS infection, and cerebral dysgenesis or genetic disorders (nonketotic hyperglycinemia, vitamin-dependent epilepsies, channelopathies). Congenital conditions that result in neuromuscular weakness and poor respiratory effort may also result secondarily in neonatal hypoxic brain injury and seizure. Such conditions might include congenital myopathies, congenital myotonic dystrophy, or spinal muscular atrophy.

In addition to CNS dysfunction, systemic organ dysfunction is noted in up to 80% of affected neonates. Myocardial dysfunction and

Table 122.8 Hypoxic-Ischemic Encephalopathy in Term Infants

SIGNS	STAGE 1 (MILD)	STAGE 2 (MODERATE)	STAGE 3 (SEVERE)
Level of consciousness	Hyperalert, responds to minimal stimuli	Lethargic	Stuporous, coma
Spontaneous activity	Normal or decreased	Decreased	None
Posture	Mild flexion of distal joints (fingers, wrist)	Distal flexion or complete extension	Decerebrated
Tone	Normal	Hypotonia (focal or general) or hypertonia	Flaccid or rigid
PRIMITIVE REFLEXES	1	2	3
Suck	Weak or incomplete	Weak or bite	Absent
Moro reflex	Intact, low threshold	Incomplete	Absent
AUTONOMIC NERVOUS SYSTEM	1	2	3
Pupils	Mydriasis	Miosis	Variable or nonreactive
Heart rate	Tachycardia	Bradycardia	Variable heart rate
Respirations	Hyperventilation	Periodic breathing	Apnea or requiring ventilation
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Adapted from Chalak L, Latremouille S, Mir I, Sánchez PJ, Sant'Anna G. A review of the conundrum of mild hypoxic-ischemic encephalopathy: current challenges and moving forward. *Early Hum Dev.* 2018;120:88–94.

cardiogenic shock, persistent pulmonary hypertension, RDS, gastrointestinal perforation, and acute kidney and liver injury are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 122.5).

The severity of neonatal encephalopathy depends on the duration and timing of injury. The need to define severity is rooted in the need to determine eligibility for *therapeutic hypothermia*, a treatment that decreases death and disability in moderate to severe HIE. A clinical grading score first proposed by Sarnat and colleagues continues to be a useful tool. Symptoms develop over hours and days, making it important to perform serial neurologic examinations (see Tables 122.7 and 122.8). Infants with moderate to severe HIE are characterized by disturbed neurologic function, altered level of consciousness, depressed tone, abnormal reflexes, and difficulty maintaining spontaneous respirations, and seizures. An empirically validated definition of mild HIE within 6 hours uses two steps: the first step is screening for fetal acidosis and acute perinatal events, and the second step has an examiner use a modified Sarnat scoring, which is expanded to include mild in addition to moderate and severe abnormalities.

DIAGNOSIS

MRI is the most sensitive imaging modality for detecting hypoxic brain injury in the neonate. Although such injury can be detected at various times and with varying pulse sequences, diffusion-weighted sequences obtained in the first 3-5 days following a presumed sentinel event are optimal for identifying acute injury (Figs. 122.6-122.9 and Table 122.9). Severe HIE is characterized on MRI by a central pattern injury that includes the thalamus, posterior limb of the internal capsule, and hippocampus with the most severe HIE resulting in involvement of the entire cortex. Magnetic resonance spectroscopy performed within first 24 hours after birth in a full-term infant is very sensitive to the severity of HIE-related brain injury. Elevated lactate/creatine ratio on day 1 of life is a predictor of adverse neurologic outcome, whereas absence of lactate predicts a normal outcome. Where MRI is unavailable or prevented by clinical instability, brain CT scans may be helpful in ruling out focal hemorrhagic lesions or large arterial ischemic strokes. Loss of gray-white differentiation and injury to the basal ganglia in more severe HIE can be detected on CT by experienced readers, but CT often misses more subtle forms of neonatal hypoxic brain injury and results in significant radiation exposure. Ultrasound has limited utility in evaluation of hypoxic injury in the term infant, but it too can be useful for excluding hemorrhagic lesions or hydrocephalus. Because of factors of size and clinical stability, ultrasound is the initial preferred (and sometimes only feasible) modality in evaluation of the preterm infant.

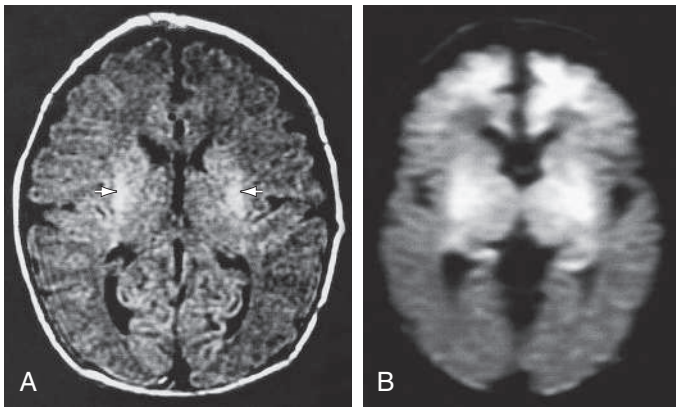

Fig. 122.6 MR images of selective neuronal injury. The infant experienced intrapartum asphyxia and had seizures on the first postnatal day. MRI was performed on the fifth postnatal day. **A,** Axial, fluid-attenuated, inversion recovery image shows increased signal in the putamen bilaterally *(arrows)* but no definite abnormality in the cerebral cortex. **B,** By contrast, a diffusion-weighted image shows striking increased signal intensity (i.e., decreased diffusion) in the frontal cortex (in addition to a more pronounced basal ganglia abnormality). (*From Volpe JJ, ed. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008. p. 420.*)

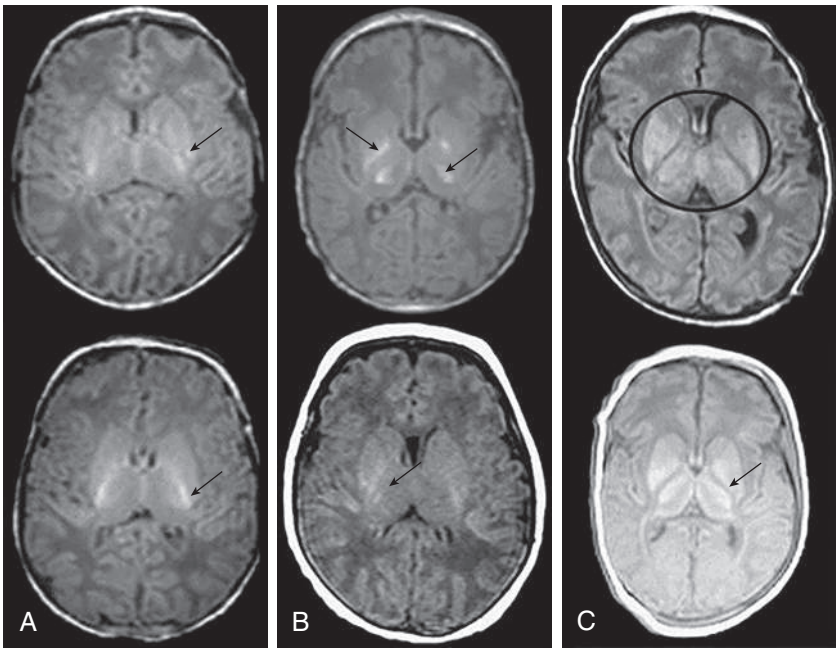

Fig. 122.7 MR images of basal ganglia/thalamic (BG/T) injury and signal intensity. *Top row,* Axial T1 weighted MR images showing mild BG/T lesions *(arrow)* **(A)**, moderate BG/T injury *(arrows)* **(B)**, and severe BG/T abnormalities *(circled)* **(C).** *Bottom row,* Axial T1 weighted MR images showing normal signal intensity (SI) in the posterior limb of the internal capsule (PLIC) *(arrow)* **(A),** equivocal, asymmetric, and slightly reduced SI in the PLIC *(arrow)* **(B),** and abnormal, absent SI in the PLIC *(arrow)* **(C).** (*From Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:675–682.*)

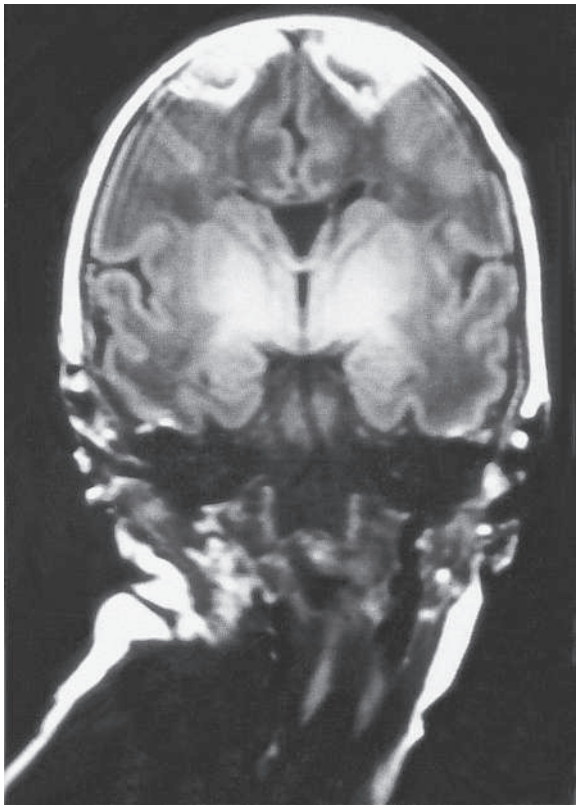

Fig. 122.8 MR image of a parasagittal cerebral injury. Coronal T1 weighted image, obtained on the fifth postnatal day in an asphyxiated term infant, shows striking triangular lesions in the parasagittal areas bilaterally; increased signal intensity is also apparent in the basal ganglia and thalamus bilaterally. (*From Volpe JJ, ed. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008. p. 421.*)

Neurophysiology Studies

Monitoring the brain of the sick newborn infant in the NICU using either multichannel electroencephalography (EEG) or limited channel amplitude integrated EEG (aEEG) may help to determine which infants are at highest risk for developmental sequelae of neonatal brain injury (Tables 122.10 and 122.11). Multichannel EEG with video is the gold standard for monitoring newborn brain function; at least 24-hour monitoring is recommended for infants at risk for seizures. The neonatal EEG contains complex spatiotemporal information and can be difficult to interpret, requiring many years in neurophysiology training. As a result, in many NICUs, EEG signal processing of a limited number of channels, with a more accessible method of data presentation, has been adopted (aEEG). Even in the absence of obvious seizures, a 24-hour multichannel EEG recording is recommended and, in infants undergoing hypothermia therapy, 72 hours is optimal to cover duration of intervention. It is known that EEG in HIE evolves following the primary HIE injury and that EEG monitoring is essential to assess this evolution and recovery. Description of EEG background grades and seizures in HIE include normal trace, which is a normal amplitude with sleep–wake cycling; mildly abnormal trace, which is a period of low amplitude and lack of sleep–wake cycling; moderately abnormal trace, which is periods of discontinuity <10 seconds; and severely abnormal trace with burst suppression pattern and discontinuity of activity for 10-60 seconds (Fig. 122.10). An aEEG is a good option if multichannel EEG is not available. The signal from biparietal electrodes is smoothed and the amplitude integrated and shows the baseline background electrical activity. A voltage classification scheme for aEEG use in HIE has been developed as follows: normal voltage (5-10 μV) and abnormal voltage (lower margin <5 μV and upper margin >10 μV).

TREATMENT

Therapeutic hypothermia, whether head cooling or systemic cooling (by servo-control to a core rectal or esophageal temperature of 33.5°C [92.3°F] within the first 6 hours after birth and maintained for 72 hours) has been shown to reduce mortality and major neurodevelopmental impairment at 18 months of age. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI, suggesting systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures than selective head cooling. The therapeutic effect of hypothermia likely results from decreased secondary neuronal injury achieved by reducing rates of apoptosis and production of mediators related to neurotoxicity. There is also benefit in seizure reduction. The therapeutic benefit of hypothermia noted at 18-22 months of age is maintained later in childhood. Once established, hypothermia may not alter the prognostic findings on MRI.

Numerous studies seeking ways to extend the benefits of therapeutic hypothermia have been attempted. The foundational clinical trials of therapeutic hypothermia had strict treatment protocols and excluded infants born before 35 or 36 weeks completed gestational weeks, those weighing <1,800 g, and infants with major congenital abnormality. Practice variation exists for offering therapeutic hypothermia to infants

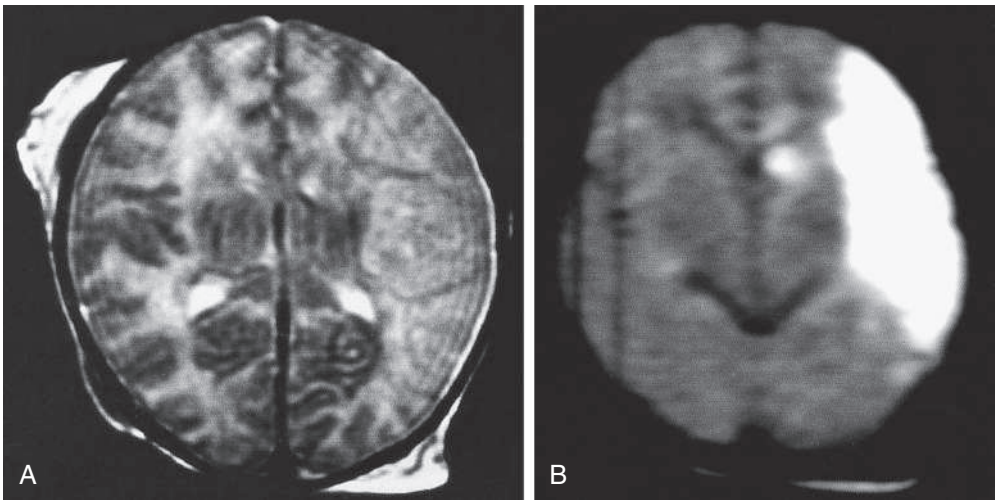

Fig. 122.9 MR images of focal ischemic cerebral injury. MRI was performed on the third postnatal day. **A,** Axial T2 weighted image shows a lesion in the distribution of the main branch of the left middle cerebral artery. **B,** Diffusion-weighted image demonstrates the lesion more strikingly. (*From Volpe JJ, ed. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008. p. 422.*)

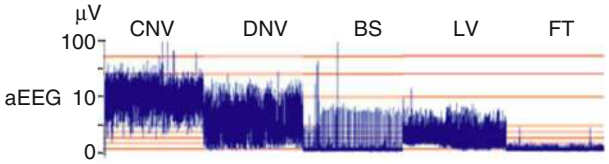

Fig. 122.10 Amplitude EEG patterns. Patterns are highlighted with pattern classification (continuous normal voltage [CNV], discontinuous normal voltage [DNV], burst suppression [BS], low voltage [LV], flat tracings [FT]). (*From Chalak L. New horizons in mild hypoxic-ischemic encephalopathy: A standardized algorithm to move past conundrum of care. Clin Perinatol. 2022;49:279–294. Fig. 3.*)

Table 122.9 Major Aspects of MRI in Diagnosis of Hypoxic-Ischemic Encephalopathy in the Term Infant

MAJOR CONVENTIONAL MR FINDINGS IN FIRST WEEK

- Cerebral cortical gray-white differentiation lost (on T1W or T2W)
- Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal peri-rolandic cortex
- Basal ganglia/thalamus, high signal (T1W and FLAIR), usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insult
- Parasagittal cerebral cortex, subcortical white matter, high signal (T1W and FLAIR)
- Periventricular white matter, decreased signal (T1W) or increased signal (T2W)
- Posterior limb of internal capsule, decreased signal (T1W or FLAIR)
- Cerebrum in a vascular distribution, decreased signal (T1W), but much better visualized as decreased diffusion (increased signal) on diffusion-weighted MRI
- **Diffusion-weighted MRI** more sensitive than conventional sequences in MRI, especially in first days after birth, when former shows decreased diffusion (increased signal) in injured areas

FLAIR, Fluid-attenuated inversion recovery; T1W and T2W, T1 weighted and T2 weighted images.
From Volpe JJ, ed. *Neurology of the Newborn.* 5th ed. Philadelphia: Elsevier; 2008: Table 9-16.

Table 122.10 Value of Electroencephalography in Assessment of Asphyxiated Term Infants

- Detection of severe abnormalities (i.e., CLV, FT, BSP) in first hours of life has a positive predictive value of an unfavorable outcome of 80–90%.
- Severe abnormalities may improve within 24 hr (~50% of BSP and 10% of CLV/FT).
- Rapid recovery of severe abnormalities is associated with a favorable outcome in 60% of cases.
- The *combination* of early neonatal neurologic examination and early aEEG enhances the positive predictive value and specificity.

aEEG, Amplitude integrated encephalography; BSP, burst suppression pattern; CLV, continuous low voltage; FT, flat trace.
From Inder TE, Volpe JJ. Hypoxic-ischemic injury in the term infant: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn.* 6th ed. Philadelphia: Elsevier; 2018: Table 20-28.

who do not meet the original study criteria, although debate for these practices also exist. A multicenter randomized clinical trial investigating the benefit of use of therapeutic hypothermia beyond 6 hours after birth reported a modest and "nonconclusive" effect. Importantly, this study extended the duration of hypothermia from 72 to 96 hours based on preclinical data suggesting that a longer period of treatment was needed at later initiation times. Assessment of deeper or longer cooling failed to show benefit in short-term outcomes, and its use is not supported by evidence nor clinically justifiable. Multicenter clinical trials are underway to assess the use of therapeutic hypothermia in preterm infants born between 33 and 35 weeks' gestation. The term "major congenital anomalies" in the original trials lead to the exclusion of numerous conditions with a favorable prognosis for survival and neurodevelopment, including trisomy 21. Unless the identified anomaly specifically imparts a medical contraindication to therapeutic hypothermia, the infant is moribund, or treatment does not align with the broader goals of care for the infant, categorical exclusion of the infant from therapeutic hypothermia solely based on the presence of one or more major congenital anomalies is likely not ethically justifiable. There have been few studies to investigate the use of therapeutic hypothermia in neonates who are beyond the perinatal period. Presently, clinical research on "targeted temperature management" in infants has been done in the pediatric intensive care setting and has little applicability to NICUs.

Complications of induced hypothermia include thrombocytopenia (usually without bleeding), reduced heart rate, and subcutaneous fat necrosis (sometimes with associated hypercalcemia) as well as the potential for overcooling and the **cold injury syndrome**. The latter is usually avoided with a servo-controlled cooling system. Therapeutic hypothermia may theoretically alter drug metabolism, prolong the QT interval, and affect the interpretation of blood gases. In clinical practice, these concerns have not been observed.

For treating seizures associated with HIE, phenobarbital continues to be used in many instances. It is typically given by intravenous loading dose (20 mg/kg). Additional doses of 5-10 mg/kg (up to 40-50 mg/kg total) may be needed. Phenobarbital levels should be monitored 24 hours after the loading dose has been given and maintenance therapy (5 mg/kg/24 hr) begun. Therapeutic phenobarbital levels are 20-40 μg/mL.

For refractory seizures, there is a high degree of variability regarding choice of a second agent. Historically, phenytoin (20 mg/kg loading dose) or lorazepam (0.1 mg/kg) have been preferred, but currently the use of levetiracetam is preferred (at times even as a first-line agent) as a second-line agent. Pharmacokinetic data suggest that due to the higher volume of distribution created by higher relative body water content in neonates, loading doses should be higher than in older children or adults. Suggested appropriate loading doses may be closer to 60 mg/kg. In addition to levetiracetam and phenytoin, other second- or third-line agents commonly used include midazolam, topiramate, and lidocaine. Pyridoxine should also be attempted, particularly in ongoing refractory seizures with highly abnormal EEG background. Status epilepticus, multifocal seizures, and need for multiple anticonvulsant medications during therapeutic hypothermia are associated with a poor prognosis.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Hyperthermia has been associated with impaired neurodevelopment and should be prevented, particularly in the interval between initial resuscitation and initiation of hypothermia. Careful attention to ventilatory status and adequate oxygenation, blood pressure, hemodynamic status, acid-base balance, and possible infection is important. Secondary hypoxia or hypotension from complications of HIE must be prevented. Aggressive treatment of seizures is critical and may necessitate continuous EEG monitoring. In addition, hyperoxia, hypocarbia, and hypoglycemia are associated with poor outcomes, so careful attention to resuscitation, ventilation, and blood glucose homeostasis is essential.

PROGNOSIS

The outcome of HIE ranges from complete recovery to death. The prognosis varies depending on the severity of the insult and the treatment. Infants with initial cord or initial (~1 hour of age) blood pH <6.7 have a 90% risk for death or severe neurodevelopmental impairment at 18 months of age. In addition, infants with Apgar scores of 0-3 at 5 minutes, high base deficit (>20-25 mmol/L), decerebrate posture, severe basal ganglia/thalamic (BG/T) lesions (Fig. 122.11; see also Fig. 122.7), persistence of severe HIE by clinical examination at 72 hours, and lack of spontaneous activity are also at increased risk for death or impairment. These predictor variables can be combined to determine a score that helps with prognosis (see Table 122.7). Infants with the highest risk are likely to die or have severe disability despite aggressive treatment, including hypothermia. Those with intermediate scores are likely to benefit from treatment. In general, severe encephalopathy, characterized by flaccid coma, apnea, absence of oculocephalic reflexes, and refractory seizures, is associated with a poor prognosis (see Table 122.8). Apgar scores alone in patients with HIE can also be associated with subsequent risk of neurodevelopmental impairment. At 10 minutes, each point decrease in Apgar score increases odds of death or disability by 45%. Death or disability occurs in 76–82% of infants with HIE with Apgar scores of 0-2 at 10 minutes. Absence of spontaneous respirations at 20 minutes of age and persistence of abnormal neurologic signs at 2 weeks of age also predict death or severe cognitive and motor deficits.

The combined use of early multichannel EEG or aEEG and MRI offers additional insight in predicting outcome in term infants with HIE (see Table 122.11). EEG or aEEG background characteristics such as pattern, voltage, reactivity, state change, and evolution after acute injury are important predictors of outcome. MRI markers include location of injury, identification of injury by certain pulse sequences, measurement of diffusivity and/or fractional anisotropy, and presence of abnormal metabolite ratios on MR spectroscopy, and all have shown

Table 122.11 Electroencephalographic Patterns of Prognostic Significance in Asphyxiated Term Infants*

ASSOCIATED WITH FAVORABLE OUTCOME
Mild depression (or less) on day 1
Normal background by day 7
ASSOCIATED WITH UNFAVORABLE OUTCOME
Predominant interburst interval >20 sec on any day
Burst suppression pattern on any day
Isoelectric tracing on any day
Mild (or greater) depression after day 12

*Associations with favorable or unfavorable outcome are generally ≥90%, but the clinical context must be considered.

From Inder TE, Volpe JJ. Hypoxic-ischemic injury in the term infant: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, Darras BT, et al., eds. *Volpe's Neurology of the Newborn*. 6th ed. Philadelphia: Elsevier; 2018: Table 20-26.

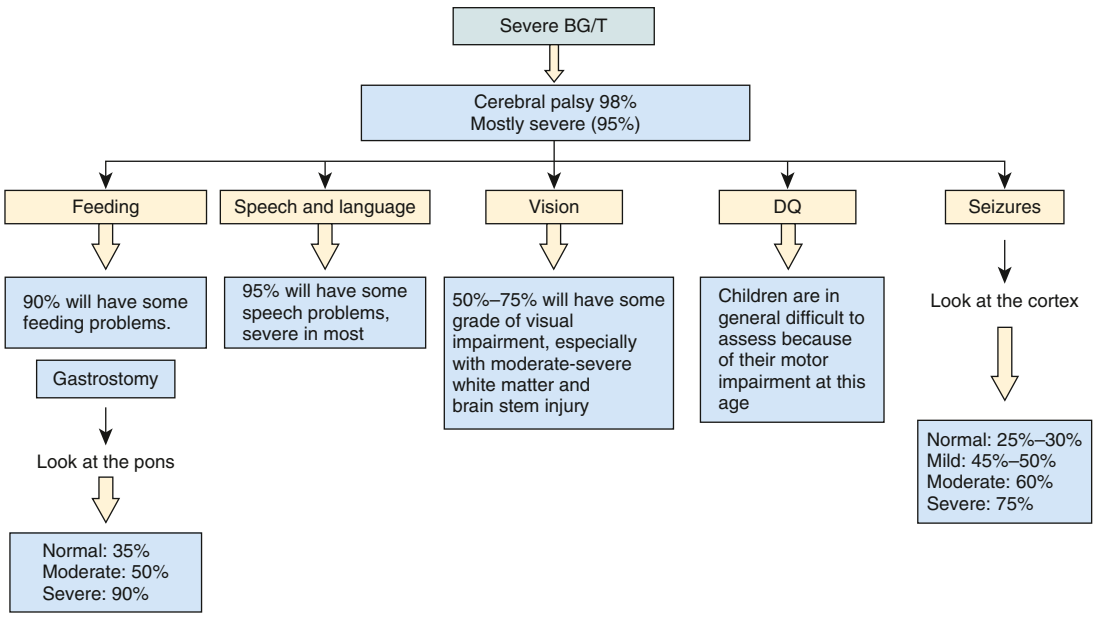

Fig. 122.11 Flow chart showing patterns of outcome with severe basal ganglia/thalamic (BG/T) injury. DQ, Developmental quotient. (*From Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy. Early Hum Dev. 2010;86:675–682.*)

correlation with outcome. Severe BG/T lesions with abnormal signal in the posterior limb of the internal capsule are highly predictive of the poorest cognitive and motor prognosis (see Fig. 122.11). Normal MRI and EEG findings are associated with a good recovery.

Microcephaly and poor head growth during the first year of life also correlate with injury to the BG/T and white matter and adverse developmental outcome at 12 months. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, and neurologic early intervention services so that the best possible outcomes can be achieved.

Brain death (death by neurologic criteria) after neonatal HIE is diagnosed from the clinical findings of coma unresponsive to pain, auditory, or visual stimulation; apnea with P_{CO_2} rising from 40 to >60 mm Hg without ventilatory support; and absence of brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, gag, sucking) (see Chapter 83). These findings must occur in the absence of hypothermia, hypotension, and elevations of depressant drugs (phenobarbital), which may take days to be metabolized and cleared completely from the blood. In the term infant, the national guideline for determination should be followed. There is no agreement on such criteria in the preterm infants. Consideration of withdrawal of life support must include discussions with the family and the healthcare team, and, if there is disagreement, an ethics committee. The best interest of the infant involves judgments about the benefits and harm of continuing therapy or avoiding ongoing futile therapy.

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122.5 Spine and Spinal Cord

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

See also Chapter 751.

Injury to the spine/spinal cord during birth is rare but can be devastating. Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral, or forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis, especially when combined with flexion and torsion of the vertical axis, may produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury occurs most often at the level of the 4th cervical vertebra with cephalic presentations and the lower cervical–upper thoracic vertebrae with breech presentations. Transection of the cord may occur *with or without* vertebral fractures; hemorrhage and edema may produce neurologic signs that are indistinguishable from those of transection, except that they may not be permanent. Areflexia, loss of sensation, and complete paralysis of voluntary motion occur below the level of injury, although the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion.

If the injury is severe, the infant, who from birth may be in poor condition because of respiratory depression, shock, or hypothermia, may deteriorate rapidly to death within several hours before any neurologic signs are obvious. Alternatively, the course may be protracted, with symptoms and signs appearing at birth or later in the first week; Horner syndrome, immobility, flaccidity, and associated brachial plexus injuries may not be recognized for several days. Constipation may also be present. Some infants survive for prolonged periods, their initial flaccidity, immobility, and areflexia being replaced after several weeks or months by rigid flexion of the extremities, increased muscle tone, and spasms. Apnea on day 1 and poor motor recovery by 3 months are poor prognostic signs.

The **differential diagnosis** of neonatal spine/spinal cord injury includes amyotonia congenita and myelodysplasia associated with spina bifida occulta, spinal muscular atrophy (type 0), spinal vascular malformations (e.g., arteriovenous malformation causing hemorrhage or stroke), and congenital structural anomalies (syringomyelia, hemangioblastoma). Ultrasound or MRI confirms the diagnosis. Treatment of the survivors is supportive, including home ventilation; patients often remain permanently disabled. When a fracture or dislocation is causing spinal compression, the prognosis is related to the time elapsed before the compression is relieved.

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122.6 Peripheral Nerve Injuries

Susan S. Cohen, Alicia J. Sprecher, and Krishna K. Acharya

See also Chapter 753.

BRACHIAL PALSY

Brachial plexus injury is a common problem, with an incidence of 0.6-4.6 per 1,000 live births. Injury to the brachial plexus may cause paralysis of the upper part of the arm with or without paralysis of the forearm or hand or, more often, paralysis of the entire arm. These injuries occur in macrosomic infants and when lateral traction is exerted on the head and neck during delivery of the shoulder in a vertex presentation, when the arms are extended over the head in a breech presentation, or when excessive traction is placed on the shoulders. The primary risk factor for brachial plexus injuries are shoulder dystocia and macrosomia (birthweight >4,000 g).

Erb-Duchenne paralysis results from injury to the nerve roots of the 5th and 6th cervical nerves, with the 7th affected in 50% of instances. The infant loses the power to abduct the arm from the shoulder, rotate the arm externally, and supinate the forearm. The characteristic position consists of adduction and internal rotation of the arm with pronation of the forearm, often described as the "waiter's tip hand." Power to extend the forearm is retained, but the biceps reflex is absent; the Moro reflex is absent on the affected side (Fig. 122.12). The outer aspect of the arm may have some sensory impairment. Power in the forearm and hand grasps is preserved unless the lower part of the plexus is also injured; the presence of hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve (in about 5% of patients), alteration in diaphragmatic excursion may be observed with ultrasound, fluoroscopy, or as asymmetric elevation of the diaphragm on chest radiograph.

Klumpke paralysis is a rare form of brachial palsy in which injury to the 7th and 8th cervical nerves and the 1st thoracic nerve produces a paralyzed hand and ipsilateral ptosis and miosis **(Horner syndrome)** if the sympathetic fibers of the first thoracic root are also injured. The incidence is as low as 0.6%, and some suggest the reason for this is modern obstetric practice and a sharp decline in the vaginal breech deliveries where there is a risk of hyperabduction of the arms. Mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury; from fracture, dislocation, or epiphyseal separation of the humerus; and from fracture of the clavicle. MRI demonstrates nerve root rupture or avulsion.

Most patients have full recovery. If the paralysis was a result of edema and hemorrhage around the nerve fibers, function should return within a few months; if it resulted from laceration, permanent damage may result. Involvement of the deltoid is usually the most serious problem and may result in **shoulder drop** secondary to muscle atrophy. In general, paralysis of the upper part of the arm has a better prognosis than paralysis of the lower part.

Treatment for **peripheral nerve injuries** consists of initial conservative management with monthly follow-up and a decision for surgical intervention by 3 months if function has not improved. Partial immobilization and appropriate positioning are used to prevent the development of contractures. In upper arm paralysis, the arm should be abducted 90 degrees with external rotation at the shoulder, full supination of the forearm, and slight extension at the wrist with the palm turned toward the face. This position may be achieved with a brace or splint during the first 1-2 weeks. Immobilization should be intermittent throughout the day while the infant is asleep and between

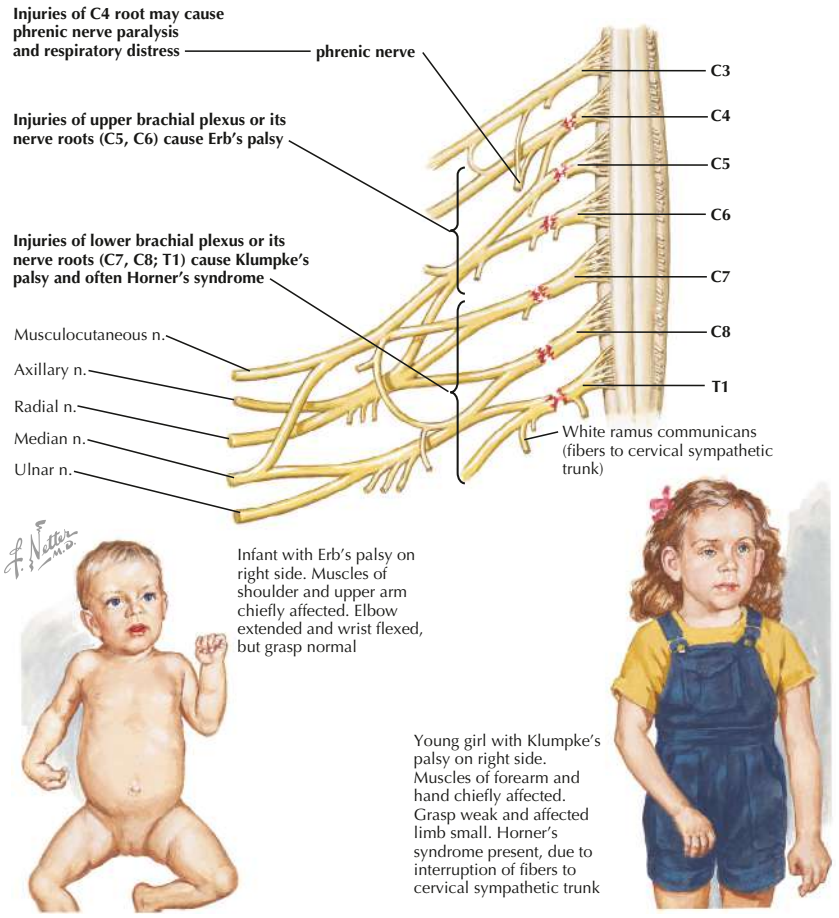

Fig. 122.12 Schematic representation of the brachial plexus with its terminal branches. The major sites of brachial plexus injury are shown. (*Courtesy Netter Images, Image ID 19943. www.netterimages.com.*)

feedings. In lower arm or hand paralysis, the wrist should be splinted in a neutral position and padding placed in the fist. When the entire arm is paralyzed, the same treatment principles should be followed. Gentle massage and range-of-motion exercises may be started by 7-10 days of age. Infants should be closely monitored with active and passive corrective exercises. If the paralysis persists without improvement for 3 months, neuroplasty, neurolysis, end-to-end anastomosis, and nerve grafting offer hope for partial recovery.

The type of treatment and the prognosis depend on the mechanism of injury and the number of nerve roots involved. The mildest injury to a peripheral nerve **(neurapraxia)** is caused by edema and heals spontaneously within a few weeks. **Axonotmesis** is more severe and is a consequence of nerve fiber disruption with an intact myelin sheath; function usually returns in a few months. Total disruption of nerves **(neurotmesis)** or root avulsion is the most severe, especially if it involves C5-T1; microsurgical repair may be indicated. Fortunately, most (75%) injuries are at the root level C5-C6, involve neurapraxia and axonotmesis, and should heal spontaneously. Botulism toxin may be used to treat biceps-triceps co-contractions.

PHRENIC NERVE PARALYSIS

Phrenic nerve injury (3rd, 4th, 5th cervical nerves) with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries, usually unilateral, are associated with ipsilateral upper brachial plexus palsies in 75% of cases. Because breathing is thoracic in type, the abdomen does not bulge with inspiration. Breath sounds are diminished on the affected side. The thrust of the diaphragm, which may often be felt just under the costal margin on the normal side, is absent on the affected side. The diagnosis is established by ultrasound or fluoroscopic examination, which reveals elevation of the diaphragm on the paralyzed side and seesaw movements of the two sides of the diaphragm during respiration. It may also be apparent on chest or abdominal radiograph.

Infants with phrenic nerve injury should be placed on the involved side and given oxygen if necessary. Some may benefit from pressure introduced by continuous positive airway pressure (CPAP) to expand the paralyzed hemidiaphragm. In extreme cases, mechanical ventilation may be needed. Initially, intravenous feedings may be needed; later, progressive gavage or oral feeding may be started, depending on the infant's condition. Pulmonary infections are a serious complication. If the infant fails to demonstrate spontaneous recovery in 1-2 months, surgical plication of the diaphragm may be indicated.

FACIAL NERVE PALSY

Facial palsy is usually a peripheral paralysis that results from pressure over the facial nerve in utero, during labor, or from forceps use during delivery. Rarely, it may result from nuclear agenesis of the facial nerve.

Peripheral facial paralysis is flaccid and, when complete, involves the entire side of the face, including the forehead. The main reported risk factors associated with traumatic facial paralysis are primigravida, birthweight >3,500 g, forceps usage, cesarean birth, and prematurity. When the infant cries, movement occurs only on the nonparalyzed side of the face, and the mouth is drawn to that side. On the affected side the forehead is smooth, the eye cannot be closed, the nasolabial fold is absent, and the corner of the mouth droops. **Central facial paralysis** spares the forehead (e.g., forehead wrinkles will still be apparent on the affected side) because the nucleus that innervates the upper face has overlapping dual innervation by corticobulbar fibers originating in bilateral cerebral hemispheres. The infant with central facial paralysis usually has other manifestations of intracranial injury, most often 6th nerve palsy from the proximity of the 6th and 7th cranial nerve nuclei in the brainstem. Prognosis depends on whether the nerve was injured by pressure or the nerve fibers were torn; improvement occurs within a few weeks in the former case. The majority of infants with traumatic facial nerve palsy will recover within the first 2 months of life. Care of the exposed eye is essential. Neuroplasty may be indicated when the paralysis is persistent. Facial palsy may be confused with absence of the depressor muscles of the mouth, which is a benign problem or with variants of Möbius syndrome.

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Chapter 123

Neonatal Resuscitation and Delivery Room Emergencies

Heidi M. Herrick and Elizabeth E. Foglia

Most infants complete the transition to extrauterine life without difficulty; however, a small proportion require resuscitation after birth (Fig. 123.1). For a newborn infant, the need for resuscitation is often caused by a respiratory problem leading to inadequate ventilation. This is in contrast to an adult cardiac arrest, which is usually caused by inadequate circulation. The goals of neonatal resuscitation are to establish adequate spontaneous respirations, obtain adequate cardiac output, and prevent the morbidity and mortality associated with hypoxic-ischemic tissue (brain, heart, kidney) injury (see Chapter 122). High-risk situations should be *anticipated* from pregnancy history and labor. Improved perinatal care and prenatal diagnosis of fetal anomalies allow for appropriate maternal transports for high-risk deliveries. Infants who are born limp, cyanotic, apneic, or pulseless require immediate resuscitation before assignment of the 1 minute Apgar score. Rapid and appropriate resuscitative efforts improve the likelihood of preventing brain damage and achieving a successful outcome.

NEONATAL RESUSCITATION

See also Chapter 79.

Recommendations for the **Neonatal Resuscitation Program (NRP)** propose an *integrated* assessment/response approach for the initial evaluation of an infant, consisting of simultaneous assessment of infant general appearance and risk factors. The fundamental principles include evaluation of the airway and establishing effective respirations and adequate circulation. The guidelines also highlight the importance of the neonatal heart rate as a primary indicator of the need for and response to resuscitation.

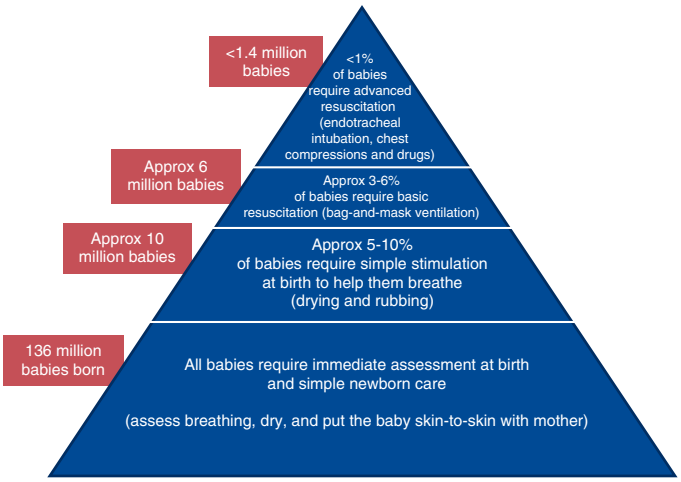

Fig. 123.1 Estimates of infants requiring resuscitation at birth. *(From Wall SN, Lee ACC, Niermeyer S, et al. Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up? Int J Gynaecol Obstet. 2009;107:S47–S64. Fig. 1.)*

Before the birth of a baby, sufficient preparation for the birth should occur. At least one individual capable of initiating neonatal resuscitation should be present at the delivery. If advanced resuscitation is anticipated, more providers should be available. Necessary equipment should be available, which routinely includes a warmer bed, blankets, infant hat, stethoscope, bulb suction, suction catheter with wall suction, bag-mask device, oxygen source with blender, pulse oximeter, laryngoscope with blade, endotracheal tubes (ETTs), laryngeal mask airway, pulse oximeter, and electrocardiogram (ECG) leads. Based on the specific details of the pregnancy, further equipment may be needed and should be readily available. The equipment should be checked to make sure it is functioning appropriately. Team members should introduce themselves, define a team leader, assign roles for the resuscitation, and discuss what actions they will take during the resuscitation. For complex resuscitations, there may be one individual whose sole job is to document the resuscitation by keeping track of time and recording interventions performed. This can help ensure the correct steps are performed in a timely manner and inform the team debriefing after resuscitation.

The umbilical cord management plan should be established before delivery. **Delayed cord clamping** after birth can be performed in both preterm and term infants. Benefits to term infants include higher hemoglobin levels at birth with improved iron stores in infancy. Benefits for preterm infants include improved hemodynamic stability, decreased need for inotropic support, and decreased red blood cell transfusions. The 2020 Neonatal Resuscitation Guidelines call for at least 30-60 seconds of delayed cord clamping after birth for vigorous term and preterm infants unless contraindications are present. It is unclear whether delayed cord clamping should be continued when an infant requires resuscitation; this is an area of active research. Umbilical cord milking should not be performed for extremely preterm infants <28 weeks' gestation because this has been associated with an increased risk of intraventricular hemorrhage.

Failure to initiate or sustain respiratory effort at birth is fairly common, with 5–10% of newborns requiring some intervention. Infants with **primary apnea** respond to stimulation by establishing normal breathing. Infants with **secondary apnea** require ventilatory assistance to establish spontaneous respiratory effort. Secondary apnea usually originates as a result of prolonged interruption of adequate oxygen delivery in the perinatal period.

Immediately after birth, all term infants should be dried, warmed, and stimulated. If the infant does not need resuscitation, these steps can occur on the mother's abdomen while delayed cord clamping is taking place. Simultaneously, the infant's tone, respiratory effort, and heart rate should be assessed (Fig. 123.2). If the infant remains apneic or bradycardic (heart rate is <100 beats/min) after stimulation, positive pressure ventilation (PPV) should be given via face mask. PPV should be initiated at peak inspiratory pressures of approximately 20 cm H_2O, positive end-expiratory pressures of 5 cm H_2O at a rate of 40-60 breaths/min.

At the same time PPV is initiated, a pulse oximeter should be placed on the right hand (preductal). Resuscitation with room air in **term infants** is effective and may reduce the risk of hyperoxia, which is associated with decreased cerebral blood flow and generation of oxygen free radicals. Room air, which is 21% fraction of inspired oxygen (F_{IO_2}), is the preferred *initial gas* for neonatal resuscitation in infants ≥35 weeks. O_2 concentration should then be titrated as needed to meet targeted peripheral oxygen saturations (>80% by 5 minutes), as defined by normal reference range by minute of life (see Fig. 123.2; see the following section on "Resuscitation of the Preterm Infant").

The most important sign of effective ventilation is a rise in heart rate. Additional signs include adequate chest rise, symmetric breath sounds, increasing O_2 saturation, spontaneous respirations, and improved tone. *If after 30 seconds of providing PPV there is no response in heart rate, corrective steps should be performed to improve ventilation.* The six

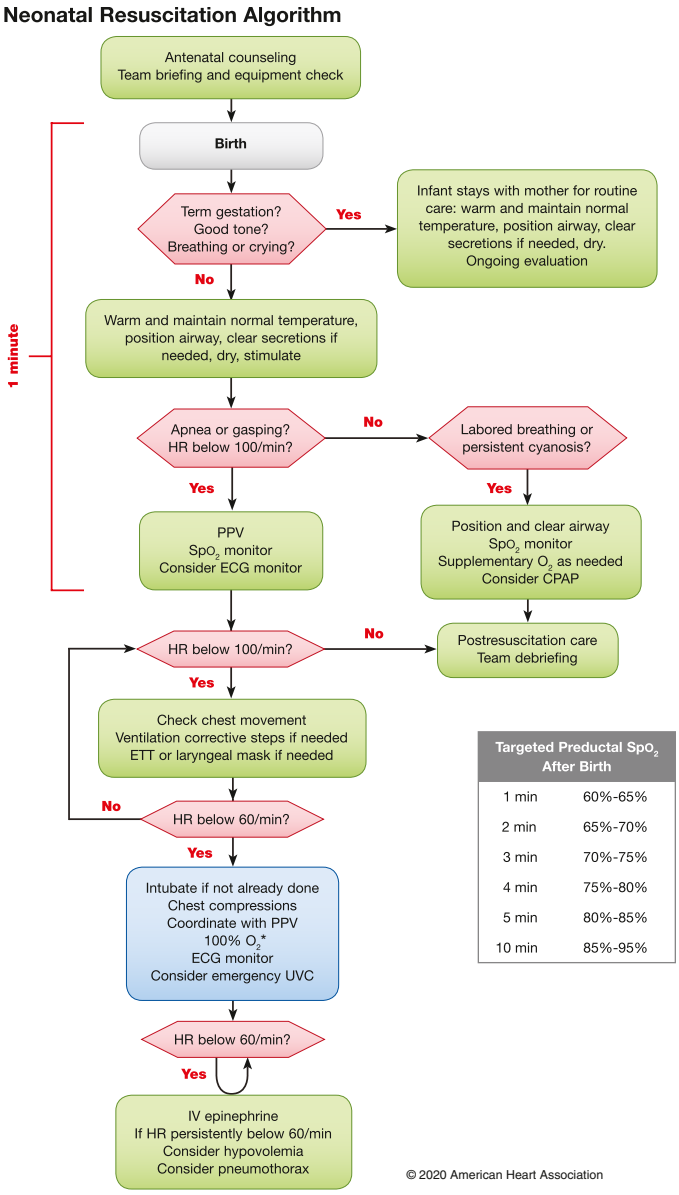

Fig. 123.2 Newborn resuscitation algorithm. CPAP, Continuous positive airway pressure; ECG, electrocardiogram; ETT, endotracheal tube; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation; UVC, umbilical venous catheter. *(From Aziz K, Lee HC, Escobedo MB, et al. Part 5: Neonatal Resuscitation: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020;142[16_suppl_2]:S524–S550. Fig. 1.)*

ventilation corrective steps can be remembered with the mnemonic **MRSOPA**: *m*ask readjustment, *r*eposition the head, *s*uction mouth and nose, *o*pen the mouth, *p*ressure increase, and *a*lternative airway.

Causes of poor response to ventilation are mask leak, airway obstruction, insufficient pressure, pleural effusions, pneumothorax, excessive air in the stomach leading to abdominal competition, hypovolemia, diaphragmatic hernia, or prolonged intrauterine asphyxia. For infants who do not respond to noninvasive PPV after corrective steps have been taken, endotracheal intubation should be performed. For infants with an otherwise normal airway weighing <1,000 g, ETT size is usually 2.5 mm; for infants 1,000-2,000 g, 3 mm; and for infants >2,000 g, 3.5 mm. A general rule for depth of insertion from upper lip in centimeters is 6 + infant's weight in kilograms. The best method to confirm accurate ETT position is exhaled CO_2 detection. A laryngeal mask airway is an alternative method to establish an airway, especially if face mask PPV is ineffective or providers skilled in intubation are unavailable.

For most infants, the underlying cause for a persistently low heart rate (<60 beats/min) is not a primary cardiac cause, but instead the result of **ineffective ventilation**. Therefore if the heart rate remains <60 beats/min after 60 seconds of PPV with corrective MRSOPA steps, the infant should be intubated (if not already done) to achieve effective ventilation. *Once the infant is intubated, if the heart rate remains <60 beats/min, chest compressions should be initiated with continued ventilation, and F_{IO_2} should be increased to 100%.* Chest compressions should be initiated over the lower third of the sternum at a rate of 90 per minute. A provider, separate from the person providing ventilation, is needed to administer chest compressions. The *thumb technique* should be used for chest compressions; the tips of both thumbs are used to depress the sternum, with the fingers on each side encircling the chest; this is the preferred method to administer chest compressions, because it has been shown to achieve a higher blood pressure, increase coronary perfusion, and result in less fatigue. In infants, regardless of whether an alternative airway has been secured, chest compressions are always coordinated with PPV. The ratio of compressions to ventilation is 3:1 (90 compressions:30 breaths). Chest compressions should continue uninterrupted for 60 seconds before reassessing heart rate to determine next steps.

Medications are rarely required, but **epinephrine** should be administered when the heart rate is <60 beats/min after 60 seconds of combined ventilation and chest compressions or during asystole. An intravenous route is recommended for epinephrine administration. The umbilical vein can generally be readily cannulated and is the preferred method for administration of medications and volume expanders during neonatal resuscitation (Fig. 123.3). An intraosseous route is another option if umbilical venous access is not obtained. Epinephrine (initial dose recommendation of 0.02 mg/kg *intravenously/intraosseously* followed by a 3-mL flush) is given for asystole or for continued heart rate <60 beats/min after 60 seconds of combined resuscitation. The dose may be repeated every 3-5 minutes. Epinephrine may also be given through the ETT (0.1 mg/kg). If adequate resuscitation continues for 20 minutes without a detectable heart rate, it is reasonable to discuss redirection of care with the team and family and to stop resuscitative efforts.

RESUSCITATION OF THE PRETERM INFANT

Resuscitation of the preterm infant should follow the same steps as a term infant, with some special considerations. Whereas resuscitation of term infants should start with room air, resuscitation of preterm infants <35 weeks' gestation should be initiated with F_{IO_2} between 21% and 30%. Pulse oximetry of the preductal (right) hand should be used to titrate O_2 concentrations for targeted saturations per the NRP algorithm (see Fig. 123.2). Most very low birthweight infants will need more than 30% once titration begins.

Special attention should be paid to *keeping the preterm infant warm in the delivery room.* Quality improvement projects have initiated bundles to improve admission temperatures of preterm infants to the neonatal intensive care unit (NICU) and have included such interventions as higher ambient temperatures in the delivery room, immediate placement of preterm infants into a plastic bag or under plastic wrap rather than drying, and exothermic mattress for resuscitation and transport of the preterm infant.

SPECIAL CIRCUMSTANCES IN THE DELIVERY ROOM

Meconium

Meconium staining of the amniotic fluid may be an indication of fetal stress. All infants born through meconium-stained amniotic fluid (regardless if the infant is vigorous or nonvigorous) should receive the same initial steps of neonatal resuscitation as infants without

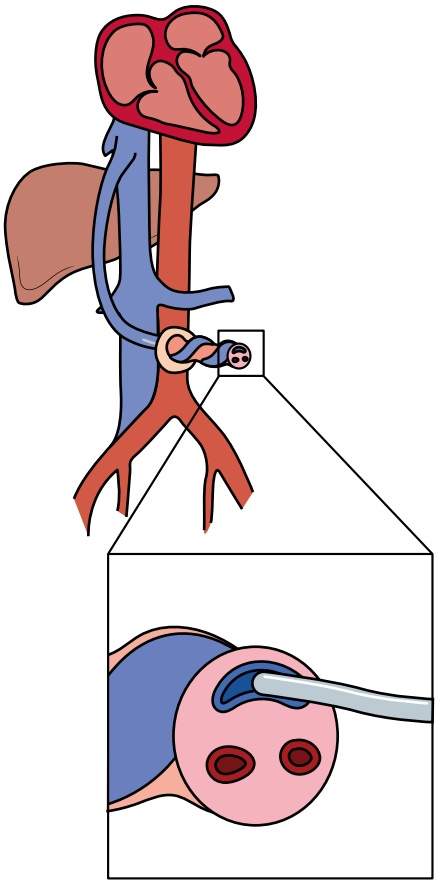

Fig. 123.3 Emergently placed umbilical venous catheter suitable for neonatal resuscitation.

meconium-stained fluid and should be assessed as any other infant. Tracheal intubation for meconium aspiration may delay the initiation of effective PPV and ultimately delay effective gas exchange and is not indicated.

Placental Abruption

Placental abruption (abruptio placentae) or uterine rupture at birth can lead to acute fetal blood loss and a hypovolemic, anemic infant at delivery. Infants can present pale and apneic with poor tone, decreased perfusion, and bradycardia. In addition to performing routine neonatal resuscitation, when an infant is suspected to be symptomatic from acute blood loss, an emergency low-lying umbilical venous catheter (UVC) or interosseous needle should be placed and emergent type O Rh-negative blood should be obtained. In acute blood loss, the blood should be administered as quickly as possible in 10 mL/kg aliquots in the delivery room. Adequate communication between obstetrics and pediatrics regarding suspected acute blood loss is crucial to early recognition and treatment of the infant.

Neonatal Encephalopathy

Infants with neonatal encephalopathy are born with abnormal neurologic function, including level of consciousness, muscle tone, apnea, and reflexes. Although there are many possible etiologies, when symptoms are accompanied by a defined perinatal event such as cord prolapse or placental abruption, hypoxic-ischemic brain injury is the presumed cause. These infants are often born with impaired respiratory drive. Immediately after initial resuscitation and stabilization, a thorough neurologic examination should be performed to assess if the infant meets formal criteria for moderate to severe encephalopathy and qualifies for therapeutic hypothermia (see Chapter 122.4).

Airway Anomalies

Hypoplasia of the mandible with posterior displacement of the tongue may result in upper airway obstruction (Pierre Robin, Stickler, DiGeorge, and other syndromes; see Chapters 118 and 357). Symptoms may sometimes be temporarily relieved by pulling the tongue or mandible forward or placing the infant in the prone position. Other rare anatomic causes of upper airway obstruction at birth include laryngeal atresia or stenosis, teratomas, hygromas, and oral tumors. Critical fetal and then neonatal airway obstruction represents an emergency in the delivery room. High-risk perinatal care has led to the more frequent prenatal diagnosis of these disorders. When diagnosed prenatally, planning can identify the location of delivery and interventions available at delivery. The **ex utero intrapartum treatment (EXIT)** procedure allows time to secure the airway in an infant known prenatally to have critical airway obstruction, before the infant is separated from the placenta (Fig. 123.4; see Chapter 118). Uteroplacental gas exchange is maintained throughout the procedure.

Pulmonary Disorders

Both congenital and acquired abnormalities can contribute to respiratory failure in the neonate. A **scaphoid abdomen** suggests a diaphragmatic hernia, as does asymmetry in contour or movement of the chest. An infant with a known diaphragmatic hernia should be immediately intubated in the delivery room and an orogastric tube placed to avoid gaseous distention of the bowel from crying or PPV. The infant should then be transferred to a tertiary referral center for surgical evaluation and treatment (see Chapter 124.1).

In infants with a prenatal diagnosis of hydrops, pleural effusions may be present at delivery, preventing adequate lung expansion and gas exchange. Similarly, infants requiring PPV in the delivery room are at risk for **pneumothorax**. Infants with pulmonary hypoplasia or meconium-stained fluid are at increased risk of this complication. Clinically, infants with a pleural effusion or pneumothorax present with respiratory distress and hypoxia, with *diminished* breath sounds on the affected side. Transillumination may be helpful to confirm the diagnosis. Emergency evacuation of a pneumothorax or pleural effusion without radiographic confirmation is indicated in an infant who is unresponsive to resuscitation efforts and has asymmetric breath sounds, bradycardia, and cyanosis. An angiocatheter attached to a stopcock and syringe should be used for evacuation. For a pleural effusion, with the infant in the supine position, the angiocatheter should be inserted in the fourth or fifth intercostal space in the anterior axillary line and directed posteriorly to evacuate the fluid. For a pneumothorax, an angiocatheter can be inserted in the fourth intercostal space in the anterior axillary line or the second intercostal space in the midclavicular line and air evacuated (see Chapter 124).

Abdominal Wall and Neural Tube Defects

Appropriate management of patients with abdominal wall defects (omphalocele, gastroschisis) in the delivery room prevents excessive fluid loss and minimizes the risk for injury to the exposed viscera. **Gastroschisis** is the more common defect, and typically the intestines are not covered by a membrane. The infant's lower body, including exposed intestines, should be gently placed in a sterile clear plastic bag after delivery. A membrane often covers an **omphalocele**, and care should be taken to prevent its rupture. The omphalocele should either be wrapped in a sterile dressing or the infant's lower body, including the omphalocele, which should be placed within a sterile bag. With both defects, a nasogastric tube should be placed, and the infant transferred to a tertiary referral center for surgical consultation and evaluation for associated anomalies (see Chapter 144).

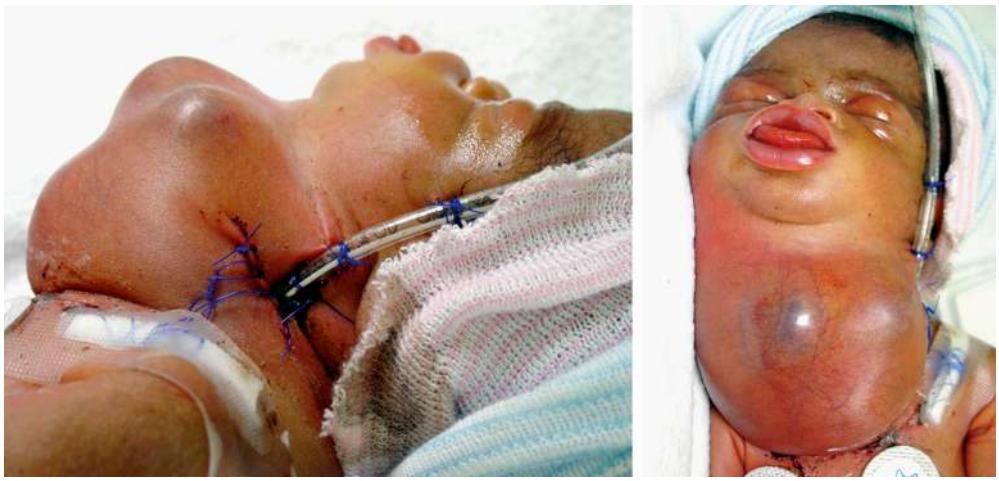

Fig. 123.4 Ex utero intrapartum therapy (EXIT) procedure. Baby with teratoma and critical high airway obstruction syndrome (CHAOS). Trachea is displaced to the lateral neck. *(Courtesy Dr. Mark Wulkan, Pediatric Surgery, Emory University.)*

Similarly, infants born with neural tube defects such as a **myelomeningocele** need special care at delivery to protect the exposed neural tube tissue from trauma and infection; infants should be placed on their side or abdomen for resuscitation. The site of the neural tube defect should be covered with a moist sterile dressing to prevent drying and infection. The infant should then be transferred to a tertiary referral center for surgical evaluation and treatment.

INJURY DURING DELIVERY

Central Nervous System

Both extracranial and intracranial birth injuries can be seen in infants after birth. **Extracranial** lesions include cephalohematoma, caput succedaneum, and subgaleal hemorrhage. **Intracranial** birth injuries include subdural hemorrhage, subarachnoid hemorrhage, and epidural hematoma. The most common intracranial injury experienced at birth is **subdural hemorrhage**, with increasing incidence seen with instrument-assisted vaginal deliveries (see Chapters 122.1 and 122.2).

Fractures

The clavicle is the most frequently fractured bone during labor and delivery. It is particularly vulnerable to injury with difficult delivery of the shoulder in the setting of **shoulder dystocia**, as well as with extended arms in breech deliveries. In the treatment of shoulder dystocia, the obstetrician may intentionally fracture the clavicle so that delivery can proceed. Symptoms of a clavicular fracture include an infant not moving the arm freely on the affected side, palpable crepitus or bony irregularity, and asymmetric or absent Moro reflex on the affected side. The prognosis for this fracture is excellent. Often, no specific treatment is needed, although in some cases the arm and shoulder on the affected side are immobilized for comfort.

Fractures of the long bones are fairly rare. Injuries often present with absent spontaneous movement of the extremity. Associated nerve involvement may also occur. Treatment involves immobilization of the affected extremity with a splint and orthopedic follow-up.

Brachial Plexus Injuries

Brachial plexus injuries result from stretching and tearing of the brachial plexus (spinal roots C5-T1) at delivery. Although shoulder dystocia is associated with an increased risk of brachial plexus injury, it can also occur during a routine delivery (see Chapter 122.6).

ONGOING CARE AFTER RESUSCITATION

The "golden hour" after a baby's birth should emphasize effective neonatal resuscitation, postresuscitation care, prevention of hypothermia (including maternal skin-to-skin contact), immediate breastfeeding if able, prevention of hypoglycemia, and therapeutic hypothermia for cases of moderate to severe neonatal encephalopathy (birth asphyxia). After supportive measures have stabilized the infant's condition, a specific diagnosis should be established and appropriate continuing treatment instituted.

For infants who receive more intensive resuscitation, a plan for ongoing monitoring and treatment should be established. These infants may experience ongoing acidosis, electrolyte abnormalities, hypo- or hyperglycemia, impaired thermoregulation, and respiratory insufficiency. If infection is suspected, appropriate antibiotics should be started as soon as possible. Severe neonatal encephalopathy may also depress myocardial function and cause cardiogenic shock despite the recovery of heart and respiratory rates. Fluids and dopamine or epinephrine as a continuous infusion should be started after initial resuscitation efforts, to improve cardiac output in an infant with poor peripheral perfusion, weak pulses, hypotension, tachycardia, or poor urine output. Regardless of the severity of neonatal encephalopathy or the response to resuscitation, asphyxiated infants should be monitored closely for signs of multiorgan hypoxic-ischemic tissue injury (see Chapter 122.4).

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Chapter 124

Transition to Newborn Pulmonary Respiration

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Successful establishment of adequate lung function at birth depends on airway patency, functional lung development, and maturity of respiratory control. Fetal lung fluid must be removed and replaced with gas. Functional residual capacity (FRC) must be established and maintained to develop a ventilation-perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood. Pulmonary blood flow increases dramatically, and the newborn must establish and maintain breathing patterns that are distinct from fetal breathing movements.

CLEARANCE OF FETAL LUNG FLUID

In utero, lung fluid is actively secreted by epithelial cells into air spaces. This fluid is essential for normal lung development and severe pulmonary hypoplasia results in infants who are unable to maintain appropriate fetal lung fluid. During birth, fluid must be cleared from the airways to allow for gas exchange. During birth, the lung epithelial cells must transition from fluid secreting to fluid absorbing.

Increased intrathoracic pressure from uterine squeeze and flexion of the infant during delivery likely contribute to movement of fluid out of the infant's nose and mouth at delivery. Additionally, inspiration decreases intrapleural pressure forming a pressure gradient that leads to the movement of fluid toward the smaller airways and ultimately out of the air spaces. As fluid moves out of the airways there is an increased interstitial hydrostatic pressure that contributes to fluid reentering the airway during each expiration until it is eventually cleared from the interstitial tissues over the course of hours.

ESTABLISHMENT OF A FUNCTIONAL RESIDUAL CAPACITY

FRC represents a balance point between collapsing and distending forces on the lung at end-expiration. Lung recoil comes from a combination of the intrinsic elasticity of the lung tissue and the surface tension within the lung. **Surfactant** plays an important role in reducing surface tension in the newborn. Premature infants and those infants with insufficient surfactant have an increased tendency toward lung collapse as observed in **respiratory distress syndrome** (see Chapter 126). Although the chest wall provides resistance to collapse in older children and adults, the highly compliant chest wall of the newborn and particularly the preterm newborn provides little resistance to lung recoil. Instead, resistance to lung collapse comes from a combination of lung tissue hydrostatic, osmotic, and oncotic pressures in addition to expiratory braking maneuvers. The neonate's expiratory braking maneuvers include adduction of the glottis and engagement of the diaphragm during expiration. Additional activities such as grunting and crying further support establishment of FRC.

INCREASED PULMONARY BLOOD FLOW

In utero, the placenta is the source of gas exchange, and blood is diverted away from the developing lungs by way of the foramen ovale and ductus arteriosus. Only 10% of the cardiac output passes through the fetal lung circulation. Following birth, blood flow to the pulmonary circulation increases due to decreasing **pulmonary vascular resistance** and closure of in utero shunts. The decline in pulmonary vascular resistance is driven by clearance of fetal lung fluid, oxygen-stimulated smooth muscle relaxation, and release of nitric oxide. Pulmonary vascular resistance decreases 50% over the first 24 hours and continues to decline over the first weeks of life. The foramen ovale is functionally closed after birth due to increased systemic vascular resistance and increased pressures in the left ventricle and left atrium. The ductus arteriosus is slower to close and ductal constriction is driven by a loss of prostaglandins from the placenta, increased oxygen exposure, and decreased local nitric oxide. Increasing pulmonary blood flow and decreasing mixing of oxygenated and deoxygenated blood after birth contributes to changing saturations in the newborn, which rise from 60% immediately after birth to over 90% by approximately 10 minutes of life (Fig. 124.1)

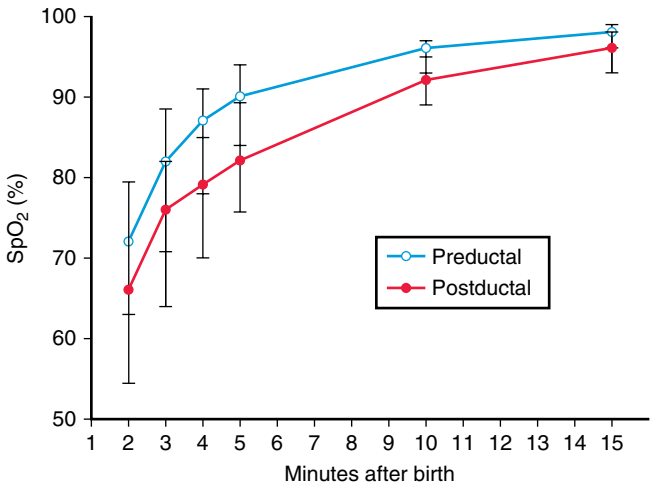

Fig. 124.1 Pre- and postductal Spo_2 levels during the first 15 minutes after birth (median; IQR). Postductal Spo_2 levels were significantly lower than preductal Spo_2 levels at 3, 4, 5, 10, and 15 minutes. *(Modified from Mariani G, Dik PB, Ezquer A, et al. Pre-ductal and post-ductal O_2 saturation in healthy term neonates after birth. J Pediatr. 2007;150:418–421.)*

BREATHING PATTERNS IN NEWBORNS

Fetal breathing movements can be observed before birth. They are generally discontinuous and generate only small tidal volumes. Following delivery, the infant must establish a regular breathing pattern with increased tidal volumes. Triggers driving this change include increased $Paco_2$, activation of chemoreceptors, and a loss of placental prostaglandins, which suppress respiratory drive. Within the fetus, low oxygen tension has an inhibitory effect on breathing. Following birth, hypoxia will eventually become a driver of respiratory effort, but in the immediate postpartum period and in the premature infant, hypoxia may depress respiratory drive.

DISORDERED TRANSITION TO PULMONARY RESPIRATION

The successful transition from placental derived oxygen delivery to pulmonary respiration requires timely completion of fetal lung fluid clearance, creation of FRC, increased pulmonary blood flow, and establishment of normal breathing patterns. Failures in any of these tasks are associated with respiratory disorders in the neonate. Failure in the timely clearance of fetal lung fluid is associated with **transient tachypnea of the newborn** (see Chapter 128). An inability to establish FRC is a feature of respiratory distress syndrome (see Chapter 126). A failure in decreasing pulmonary vascular resistance causes persistent pulmonary hypertension of the newborn (see Chapter 130) and in infants without appropriate respiratory patterns, **apnea** (see Chapter 125) is a presenting concern.

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Chapter 125

Apnea

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Apnea is a prolonged cessation of respiration and must be distinguished from *periodic breathing* because apnea is often associated with serious illness. Although there is no universal agreement, apnea is usually defined as cessation of breathing for a period of ≥20 seconds, or a period <20 seconds that is associated with a change in tone, pallor, cyanosis, or bradycardia (<80-100 beats/min). Based on the absence of respiratory effort and/or airflow, apnea can be obstructive, central, or mixed. **Obstructive apnea** is characterized by absence of airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration, or it may result from incoordination of the tongue and other upper airway muscles involved in maintaining airway patency. **Central apnea** is caused by decreased central nervous system (CNS) stimuli to respiratory muscles and results in both airflow and chest wall motion being absent. Gestational age (GA) is the most important determinant of respiratory control, with the frequency of central apnea being inversely related to GA. The immaturity of the brainstem respiratory centers is manifest by an attenuated response to CO_2 and a paradoxical response to hypoxia that results in central apnea rather than hyperventilation. Mixed apnea is most often observed in apnea of prematurity with obstructive apnea preceding central apnea. Short episodes of apnea are usually central, whereas prolonged ones are often mixed.

OBSTRUCTIVE APNEA

Obstructive apnea derives from interrupted upper airway flow. Causes of obstructive apnea can largely be divided into anatomic abnormalities and neuromuscular abnormalities.

Craniofacial disorders are a common cause of obstructive apnea of the newborn. Micrognathia, retrognathia, or Pierre Robin sequence all cause upper airway obstruction due to backward dislodgement of the tongue into the airway. This obstruction may be improved by prone positioning of the neonate. Although cleft lip and palate are not always associated with obstructive apnea, infants with these conditions are at risk for apnea related to abnormal narrowing of the upper airway structures. Additional anatomic abnormalities that can contribute to obstructive apnea include narrowing or occlusion of the nasal passages (i.e., choanal atresia) or narrowing of the airways (i.e., laryngomalacia). Many causes of anatomic obstruction are syndromic and include skeletal dysplasia, VACTERL association, Joubert syndrome, CHARGE syndrome, DiGeorge syndrome, and Stickler syndrome.

Neuromuscular weakness can contribute to **obstructive apnea** via airway collapse in the setting of low tone. Additionally, respiratory muscle weakness may impede the infant from overcoming normal airway resistance.

CENTRAL APNEA

Central apnea has a wide range of etiologies and should always lead to a diagnostic evaluation as it can often be an early warning sign of clinical decompensation. Table 125.1 provides a framework for the disease processes that can contribute to apnea. Infection or metabolic derangements should always be considered as an etiology for infants with new or worsening apnea. Abnormal CNS control of breathing can be related to prematurity, but other CNS abnormalities including injury or malformation can contribute to central apnea. **Congenital central hypoventilation syndrome** is a rare permanent genetic cause of central apnea that begins in the neonatal period (see Chapter 468.2).

APNEA OF PREMATURITY

Apnea in preterm infants is defined as cessation of breathing for ≥20 seconds or for any duration if accompanied by cyanosis and bradycardia (<80-100 beats/min). The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia. Short apnea episodes (10 seconds) are rarely associated with bradycardia, whereas longer episodes (>20 seconds) have a higher incidence of bradycardia. Bradycardia follows the apnea by 1-2 seconds in >95% of cases and is most often sinus. Vagal responses and rarely heart block are causes of bradycardia *without* apnea. Short, self-resolving oxygen desaturation episodes noted with continuous monitoring are normal in neonates, and treatment is not necessary.

Apnea of prematurity results from immature respiratory control, most frequently occurs in infants <34 weeks of GA, and occurs in the absence of identifiable predisposing diseases. The incidence of apnea of prematurity varies inversely with GA. Apnea of prematurity is almost universal in infants born at <28 weeks of GA, and the incidence rapidly decreases from 85% of infants <30 weeks of GA to 20% of infants <34 weeks of GA. The onset of apnea of prematurity can be during the initial days to weeks of age but is often delayed if there is respiratory distress syndrome (RDS) or other causes of respiratory distress. In premature infants without respiratory disease, apneic episodes can occur throughout the first 7 postnatal days with equal frequency. In infants with apnea of prematurity, the events decline significantly by 34 weeks corrected GA. Resolution may be delayed in infants with **bronchopulmonary dysplasia** (see Chapter 127) because of poorer reserves and an increased incidence of subglottic stenosis, laryngomalacia, or tracheomalacia, which can contribute to **obstructive apneas**.

Table 125.1 Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), transient following general anesthesia, congenital central hypoventilation syndrome
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, paradoxical response to hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center (prematurity); sleep state; sudden unexpected postnatal collapse

Preterm infants born at <35 weeks of GA are at risk for apnea of prematurity and therefore should receive cardiorespiratory monitoring. Apnea that occurs in the absence of other clinical signs of illness in the first 2 weeks in a preterm infant is likely apnea of prematurity; therefore additional evaluation for other etiologies is often unwarranted. However, *the onset of apnea in a previously well preterm neonate after the second week of life is a critical event that may be associated with serious underlying pathology*. Prompt investigation for sepsis/meningitis, medication side effects, metabolic derangements, structural CNS anomalies, intracranial hemorrhage, or seizures is warranted.

TREATMENT

Observation is the most common treatment strategy for infants with **obstructive apnea,** and temporizing measures including prone positioning can help to minimize symptoms until sufficient patient growth alleviates the obstruction. The use of supplemental oxygen, **nasal continuous positive airway pressure (nCPAP),** or bilevel positive airway pressure may facilitate stenting of airways and limit obstructive events. Surgical interventions depend on the underlying cause and include supraglottoplasty, palatoplasty, tongue-lip adhesion, tongue base reduction, nasal stent, mandibular distraction, and in severe cases, tracheostomy to bypass areas of obstruction.

For apnea of prematurity, gentle tactile stimulation, or provision of flow and/or supplemental oxygen by nasal cannula, is often adequate therapy for mild and intermittent episodes. **nCPAP** (3-5 cm H_2O) and **high-flow nasal cannula** (**HFNC**; 1-4 L/min) are appropriate therapies for **mixed** or **obstructive apnea**. The efficacy of both nCPAP and HFNC is related to their ability to splint the upper airway to prevent airway obstruction. Additionally, the maintenance of a higher functional residual capacity can decrease the duration of **central apnea**. Both are used widely, but nCPAP may be preferred in extremely preterm infants because of its proven efficacy and safety.

Recurrent or persistent apnea of prematurity is effectively treated with methylxanthines. **Methylxanthines** increase central respiratory drive by lowering the threshold of response to hypercapnia as well as enhancing contractility of the diaphragm. **Caffeine** and **theophylline** are similarly effective methylxanthines, but caffeine is preferred because of its longer half-life and lower potential for side effects (less tachycardia and feeding intolerance). In preterm infants, caffeine reduces the incidence and severity of apnea of prematurity, facilitates successful extubation from mechanical ventilation, reduces the rate of bronchopulmonary dysplasia (see Chapter 127), and improves neurodevelopmental outcomes. Caffeine therapy can be safely administered orally (PO) or intravenously (IV). Generally, infants are given an initial loading dose of 20 mg/kg of caffeine citrate followed 24 hours later by once-daily maintenance doses of 5-10 mg/kg. Because the therapeutic window is wide and serious side effects associated with caffeine are rare, monitoring of serum drug concentrations is usually unnecessary. Monitoring is primarily through observation of vital signs (tachycardia) and clinical response. Higher doses of caffeine may be more effective without serious adverse events, but additional studies are needed to ensure safety. Studies suggest that early initiation of caffeine, in the first 3 days of life, in extremely preterm infants improves outcomes. However, it is reasonable to delay caffeine therapy until apnea occurs in older infants. Caffeine therapy is usually continued until an infant is free of clinically significant apnea or bradycardia for 5-7 days without positive pressure respiratory support, or at 34 weeks' postmenstrual age (PMA).

In an infant with significant anemia, transfusion of packed red blood cells (RBCs) increases blood O_2-carrying capacity, improves tissue oxygenation, and may be associated with a short-term reduction in apnea. However, a long-term benefit with regard to apnea appears unlikely.

Gastroesophageal reflux (GER) is common in neonates, but despite being associated with apnea anecdotally, data do not support a causal relationship between GER and apneic events. In preterm infants, medications that inhibit gastric acid production have potentially harmful side effects (increased incidence of sepsis, necrotizing enterocolitis, death) and may increase the incidence of apnea and bradycardia. Therefore the routine use of medications that inhibit gastric acid synthesis or promote gastrointestinal motility to reduce the frequency of apnea in preterm infants should be discouraged. Antireflux treatment does correlate with decreased rates of obstructive apnea; however, this does not seem to be a causal relationship. Feeding strategies including more frequent or slower/longer feedings may be considered. Thickening feedings with xanthan gum is linked to late-onset necrotizing enterocolitis and should not be attempted. Other thickeners (i.e., rice) are not nutritionally appropriate for the preterm infant. The use of elemental or extensively hydrolyzed formulas can decrease transit time and may decrease symptoms of GER and can be considered in age-appropriate populations.

PROGNOSIS

In 92% of infants by 37 weeks' PMA and in 98% of infants by 40 weeks' PMA, apnea of prematurity resolves spontaneously. However, infants born well before 28 weeks' GA may experience apnea and bradycardic events until 44 weeks' PMA. Beyond 44 weeks' PMA, extreme events (apnea >30 seconds and/or bradycardia <60 beats/min for >10 seconds) are very rare. The period that an infant should be observed to ensure resolution of apnea and bradycardia is not defined and among institutions is highly variable. However, many experts would recommend that an infant demonstrate an event-free period of 5-7 days before discharge. Although the nature and severity of events should dictate the length of observation, sufficiently large retrospective cohort studies suggest that a 1–3-day (infants born at ≥30 weeks' GA), 9–10-day (27-28 weeks' GA), or 13–14-day (<26 weeks' GA) event-free period predicts resolution of apnea in up to 95% of infants successfully. Brief, isolated bradycardic episodes associated with oral feeding are common in preterm infants and are generally not considered significant during the event-free period.

Despite its high frequency in preterm infants, the harm associated with apnea of prematurity is unknown. However, apnea of prematurity does not appear to alter an infant's prognosis unless it is severe, recurrent, and refractory to therapy. Prompt, effective therapy and careful monitoring are vital to avoid prolonged, severe hypoxia, which may increase the risk of death and neurodevelopmental impairment.

Sudden Infant Death Syndrome and Home Monitoring

Although preterm infants are at higher risk for sudden infant death syndrome (SIDS), apnea of prematurity *does not* further increase that risk. The epidemiologic evidence that placing babies supine during sleep reduces the rate of SIDS deaths by >50% suggests that positioning, and not prematurity, primarily influences the incidence of SIDS. Supine positioning on a firm sleep surface separate from the parents' bed, promotion of breastfeeding, and pacifier use during sleep reduce the incidence of SIDS. Avoidance of cigarette smoke exposure and no parental use of alcohol or illicit drugs during pregnancy and after birth are also important in the prevention of SIDS.

In-home monitoring is an area that has received significant interest in prevention of SIDS. In a large cohort study, episodes of apnea and bradycardia were not uncommon (severe events detected in 10% of infants monitored and 2.3% of healthy term infants). Preterm infants remained at risk for apnea until approximately 43 weeks' PMA; however, most SIDS deaths occurred after apnea has resolved occurring at an average of 45.8 weeks' PMA for premature infants and 52.3 weeks' PMA for term infants. There was no evidence that home monitoring impacted the incidence of SIDS. The role for home monitors is likely limited to premature infants with prolonged or extreme episodes of apnea (and should be discontinued after 44 weeks' PMA in this population), infants with specific risk factors for obstructive apnea, or requiring supplemental oxygen or mechanical ventilation.

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Chapter 126

Respiratory Distress Syndrome (Hyaline Membrane Disease)

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

INCIDENCE

Respiratory distress syndrome (RDS) occurs primarily in premature infants; its incidence is inversely related to gestational age (GA) and birthweight. It occurs in 60–80% of infants <28 weeks' GA, in 15–30% of those between 32 and 36 weeks' GA, and rarely in those >37 weeks' GA. The risk for development of RDS increases with maternal diabetes, multiple births, cesarean delivery, precipitous delivery, asphyxia, cold stress, and a maternal history of previously affected infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal opiate use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

ETIOLOGY AND PATHOPHYSIOLOGY

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. In the absence of pulmonary surfactant, significantly increased alveolar **surface tension** leads to atelectasis, and the ability to attain an adequate **functional residual capacity (FRC)** is impaired. Additionally, insufficient surfactant contributes to heterogenous lung expansion with atelectatic areas remaining unventilated and progressive overdistension of ventilated regions according to Laplace's law (Fig. 126.1).

Although surfactant is present in high concentrations in fetal lung by 20 weeks of gestation, it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 weeks. Mature levels of pulmonary surfactant are present usually after 35 weeks of gestation. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, SP-B, SP-C, and SP-D), and cholesterol (Fig. 126.2). With advancing GA, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells (Fig. 126.3). These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability at end-expiration. Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high O_2 concentrations and mechanical ventilation, thereby further reducing secretion of surfactant.

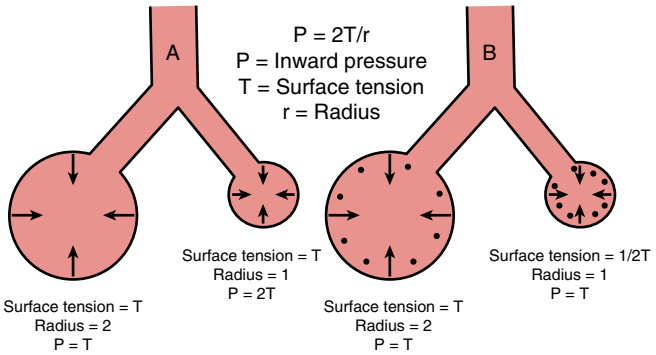

Fig. 126.1 Laplace's law as it applies to alveolar distension. Laplace's law states that the collapsing pressure in the alveolus is directly related to **surface tension** and inversely related to alveolar radius. In **A** the collapsing pressure is higher in the smaller alveoli thus the smaller alveolus further collapses, and larger alveolus distends leading to asymmetry in ventilation. In **B** with **surfactant** present, the particles become more densely spaced as the alveolus collapses, which decreases **surface tension**, and the resulting collapsing pressure is equalized between the two alveoli.

Atelectasis results in perfused but not ventilated alveoli, causing hypoxia. Decreased lung compliance, small tidal volumes, increased physiologic dead space, and insufficient alveolar ventilation eventually result in hypercapnia. The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself. Progressive injury to epithelial and endothelial cells results from atelectasis (atelectrauma), volutrauma, ischemic injury, and oxygen toxicity. This injury leads to effusion of proteinaceous material and cellular debris into the alveolar spaces (forming the classic hyaline membranes) further impairing oxygenation. RDS represents a vicious cycle of diminished surfactant production, worsening atelectasis, lung injury, and severe hypoxia (Fig. 126.4).

CLINICAL MANIFESTATIONS

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants, until rapid, shallow respirations and cyanosis become more obvious. A later onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with birthweight <1,000 g). Characteristically, tachypnea, prominent (often audible) expiratory grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis are noted. Breath sounds may be normal or diminished with a harsh tubular quality, and on deep inspiration, fine crackles may be heard. *The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated,* blood pressure may fall; *cyanosis and pallor increase, and grunting decreases or disappears, as the condition worsens. Apnea and irregular respirations are ominous signs requiring immediate intervention.* Untreated patients develop a mixed respiratory-metabolic acidosis with hypoxia and the potential to progress to respiratory failure with multisystem organ dysfunction due to inadequate oxygen delivery. In most cases, the signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired O_2 levels and/or lower ventilator support. Death can result from severe impairment of gas exchange, pulmonary air leaks (pulmonary interstitial emphysema, pneumothorax; see Chapter 132), pulmonary hemorrhage (see Chapter 133), or intraventricular hemorrhage (IVH).

DIAGNOSIS

The clinical course, chest x-ray findings, and blood gas values help establish the clinical diagnosis. On chest radiograph, the lungs may have a characteristic but not pathognomonic appearance that includes low lung volumes, a diffuse, fine reticular granularity of the parenchyma (ground-glass appearance), and air bronchograms (Fig. 126.5). The initial x-ray appearance is occasionally normal, with the typical pattern developing during the first day. Considerable variation in radiographic findings may be seen, especially in infants who have already received treatment with surfactant replacement and/or positive pressure respiratory support; this variation often results in poor correlation between radiographic findings and the clinical course. Blood gas findings are characterized initially by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

In the differential diagnosis, early-onset sepsis may be indistinguishable from RDS. In neonates with pneumonia, the chest radiograph may be identical to that for RDS. Clinical factors such as maternal group B streptococcal colonization with inadequate intrapartum antibiotic prophylaxis, maternal fever (>38.5°C) or chorioamnionitis, or prolonged

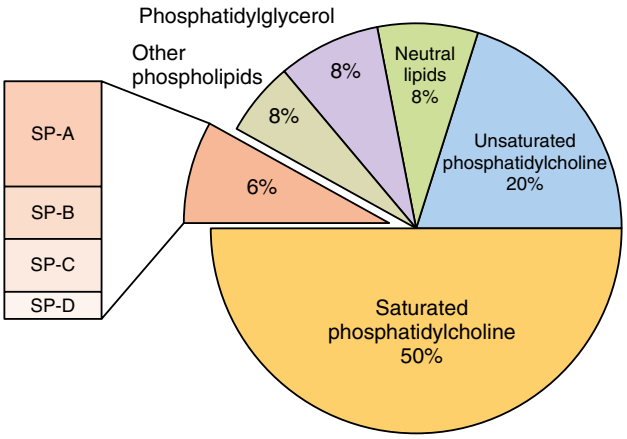

Fig. 126.2 Composition of surfactant. SP-A, Surfactant-associated protein A; SP-B, surfactant-associated protein B; SP-C, surfactant-associated protein C; SP-D, surfactant-associated protein D. *(From Jobe AH, Ikegami M. Biology of surfactant. Clin Perinatol. 2001;28:655–669.)*

rupture of membranes (>18 hours) are associated with an increased risk of early-onset sepsis. Although complete blood counts are neither sensitive nor specific in the diagnosis of early-onset sepsis, the presence of marked neutropenia has been associated with increased risk. **Transient tachypnea of the newborn** (TTN; see Chapter 128) is a common consideration that may be distinguished from RDS by its shorter and milder clinical course and is characterized by low or no need for O_2 supplementation. Cyanotic congenital heart disease (in particular, total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color-flow imaging can be performed in infants who show no response to surfactant replacement, to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance (PVR). Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions, and congenital anomalies (pulmonary congenital airway malformations, pulmonary lymphangiectasia, diaphragmatic hernia, lobar emphysema) must be considered in patients with an atypical clinical course but can generally be differentiated from RDS through radiographic and other evaluations (Fig. 126.6).

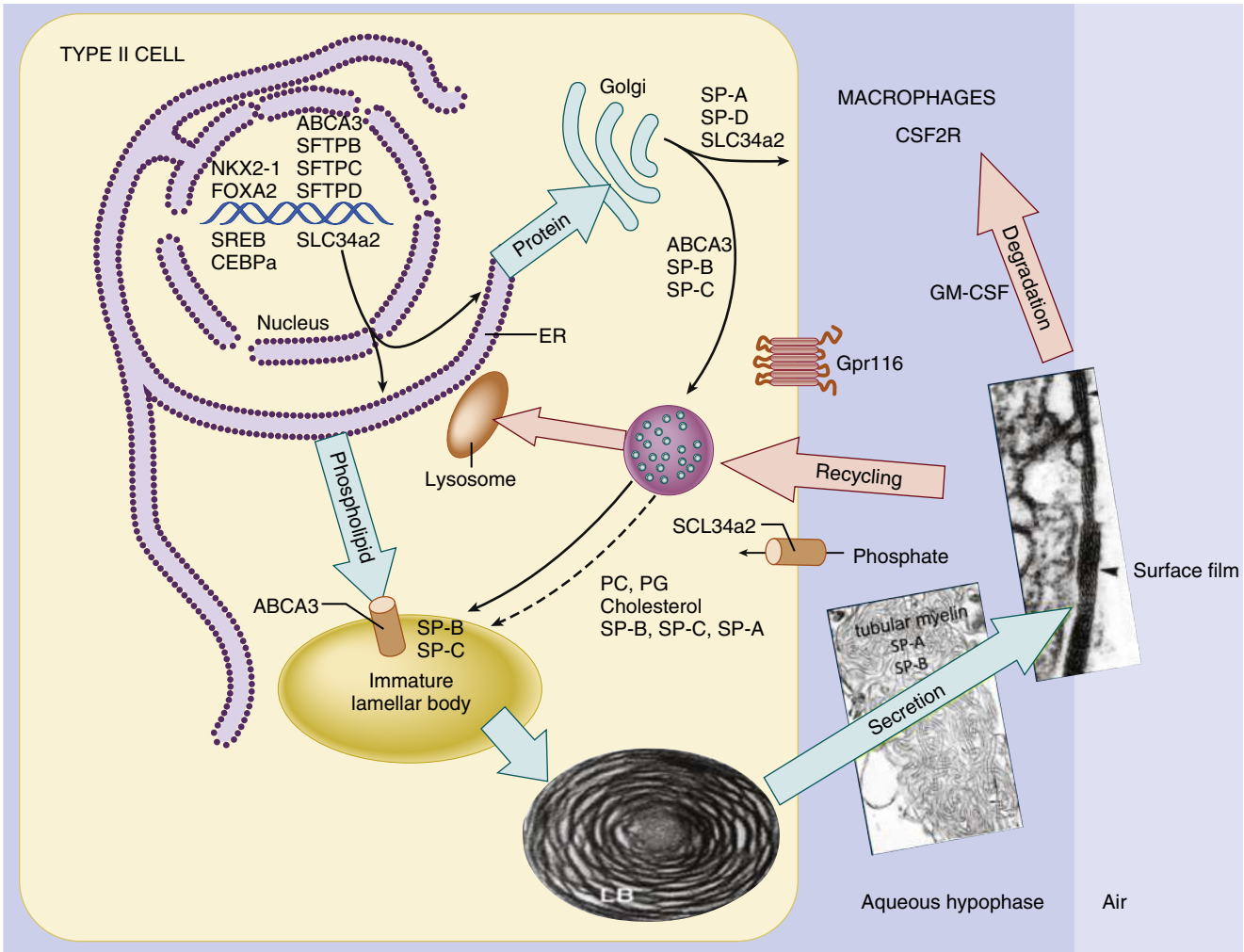

Fig. 126.3 Biosynthesis of surfactant involves distinct pathways for surfactant proteins and lipids. SP-B and SP-C are trafficked from the endoplasmic reticulum (ER) to lamellar bodies via the Golgi complex and multivesicular body (MVB); in contrast, surfactant phospholipids are likely directly transported from the ER to specific lipid importers (ABCA3) in the lamellar body–limiting membrane. Surfactant proteins and lipids are assembled into bilayer membranes that are secreted into the alveolar airspace, where they form a surface film at the air–liquid interface. Cyclical expansion and compression of the bioactive film results in the incorporation and loss of lipids and proteins from the multilayered surface film. Surfactant components removed from the film are degraded in alveolar macrophages or are taken up by type II epithelial cells for recycling or degradation in the lysosome. The MVB plays a key part in the integration of pathways for surfactant synthesis, recycling, and degradation. NKX2-1, FOXA2, SREBP, and CEBPα are transcription factors regulating surfactant protein and lipid synthesis. SLC34a2 is a phosphate transporter. Gpr116 is a membrane receptor regulating surfactant secretion. ABCA3, ATP-binding cassette transporter A3; GM-CSF, granulocyte-macrophage colony-stimulating factor; PC, phosphatidylcholine; PG, phosphatidylglycerol; SP, surfactant proteins. *(From Polin RA, Abman SH, Rowitch DH, Benits WE, eds. Fetal and Neonatal Physiology, 6th ed. Philadelphia: Elsevier; 2022: Fig. 75.3.)*

Although rare, genetic disorders may contribute to respiratory distress. Abnormalities in **surfactant protein B and C** genes as well as a gene responsible for transporting surfactant across membranes, ABC transporter 3 *(ABCA3)*, are associated with severe and often lethal familial respiratory disease. **Congenital alveolar proteinosis** (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants (see Chapter 434). In atypical cases of RDS, a lung profile (lecithin:sphingomyelin ratio and phosphatidylglycerol determination) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency. Other familial causes of neonatal respiratory distress (not RDS) include mucopolysaccharidosis, acinar dysplasia, pulmonary lymphangiectasia, and alveolocapillary dysplasia. Evaluation for these disorders should be pursued with the assistance of pediatric pulmonologists and geneticists. Evaluation may include lung imaging, fluid sampling, tissue biopsy, and genetic testing.

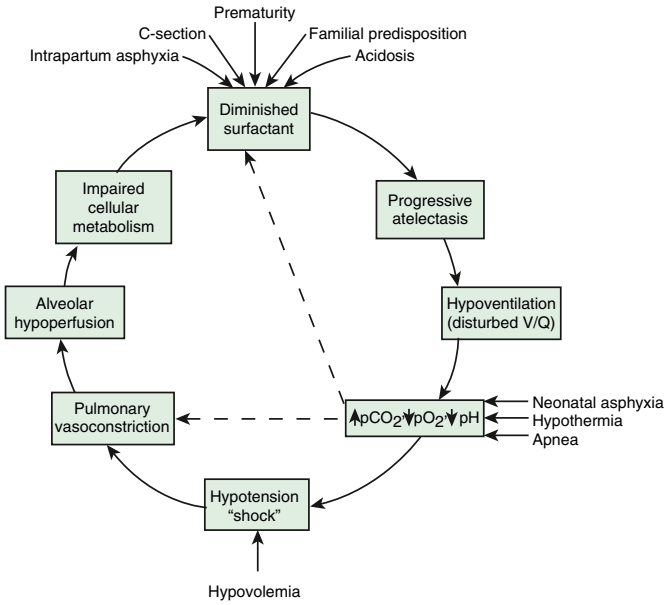

Fig. 126.4 Contributing factors in the pathogenesis of hyaline membrane disease. The potential "vicious circle" perpetuates hypoxia and pulmonary insufficiency. V/Q, Ventilation-perfusion ratio. *(From Farrell P, Zachman R. Pulmonary surfactant and the respiratory distress syndrome. In Quilligan EJ, Kretchmer N, eds. Fetal and Maternal Medicine. New York: Wiley; 1980.)*

PREVENTION

Avoidance of unnecessary or poorly timed early (<39 weeks' GA) cesarean delivery or induction of labor and appropriate management of high-risk pregnancy and labor (including administration of antenatal corticosteroids) are important preventive strategies. Strategies to prevent preterm birth include antenatal use of progesterone; measurement of cervical length and cerclage placement as indicated; and use of antibiotics, tocolytics, and magnesium for threatened preterm labor. In cases where premature delivery cannot be avoided, the transfer of the mother to an institution with appropriate neonatal care capabilities can improve early management of RDS. Antenatal and intrapartum fetal

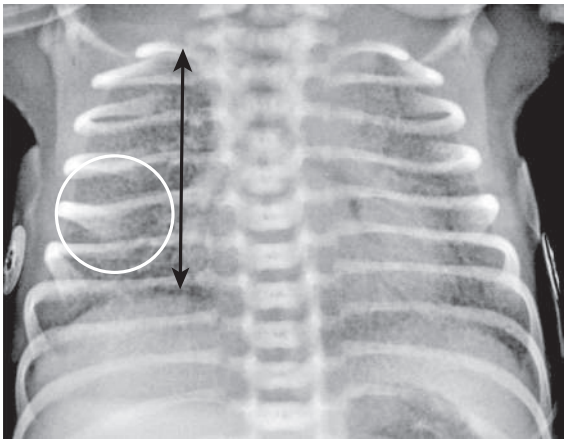

Fig. 126.5 Respiratory distress syndrome (RDS) of the newborn (hyaline membrane disease [HMD]). There is a diffuse ground-glass or finely granular appearance *(circle)* in a bilateral and symmetric distribution. Hypoaeration is seen in nonventilated lungs *(double arrow)*. *(From Herring W. Learning Radiology: recognizing the Basics, 4th ed. Philadelphia: Elsevier; 2020: Fig. 28.2.)*

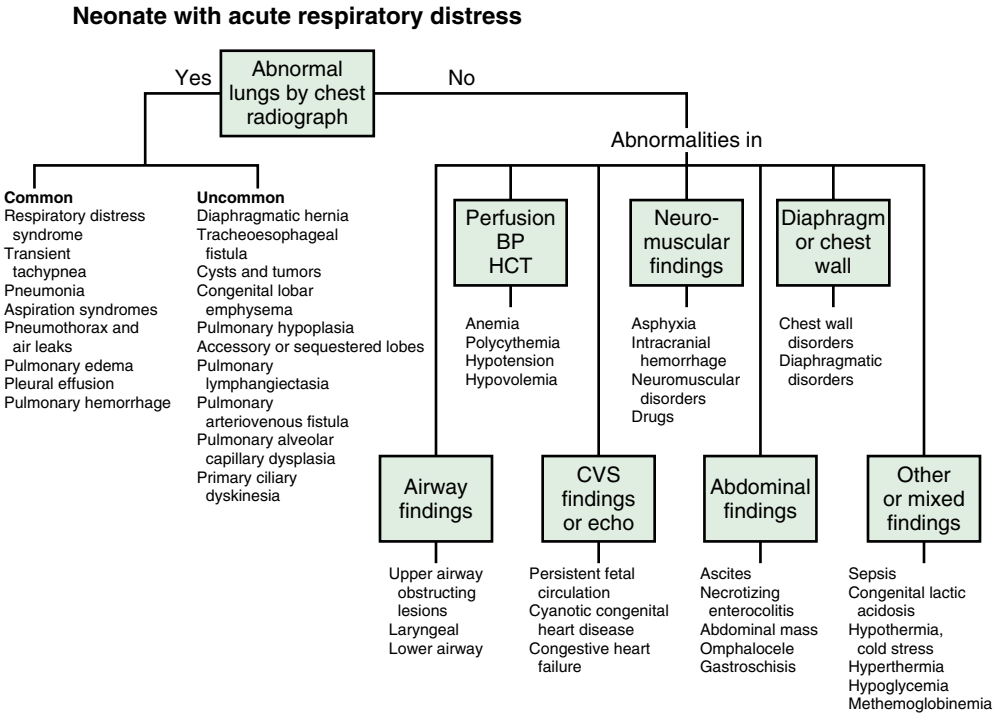

Fig. 126.6 Neonate with acute respiratory distress. BP, Blood pressure; CVS, chorionic villus sampling; HCT, hematopoietic cell transplant. *(From Battista MA, Carlo WA. Differential diagnosis of acute respiratory distress in the neonate. In Frantz ID, ed. Tufts University of School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases. Vol. 2. Issue 3. Newtown, PA: Associates in Medical Marketing Co.; 1992.)*

monitoring may decrease the risk of fetal asphyxia; asphyxia is associated with an increased incidence and severity of RDS.

Administration of **antenatal corticosteroids** to women before 37 weeks of gestation significantly reduces the incidence and mortality of RDS as well as overall neonatal mortality. Antenatal corticosteroids also reduce (1) overall mortality, (2) admission to the neonatal intensive care unit (NICU) and need for/duration of ventilatory support, and (3) incidence of severe IVH, necrotizing enterocolitis (NEC), and neurodevelopmental impairment. Betamethasone and dexamethasone have both been used antenatally. The American College of Obstetricians and Gynecologists (ACOG) recommends antenatal corticosteroids for all women presenting between 24- and 34-weeks' gestation in preterm labor. Antenatal corticosteroid use before 24 weeks' gestation for preterm labor or rupture of membranes should be driven by the family's preferences for intervention. ACOG recommends a single course of antenatal corticosteroid for mothers presenting between 34- and 36-weeks' gestation in preterm labor if no previous steroids have been given during the pregnancy. One repeat course of antenatal corticosteroids may be considered for mothers at risk of preterm delivery more than 14 days from the prior course of steroids and with a GA less than 34 weeks. Additional repeat courses of antenatal corticosteroids are not recommended due to impact on birthweight, cerebral myelination, and lung growth. Antenatal corticosteroids do not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis.

TREATMENT

The basic defect requiring treatment in RDS is inadequate pulmonary O_2-CO_2 exchange. Basic supportive care (thermoregulatory, circulatory, fluid, electrolyte, and respiratory) is essential while FRC is established and maintained. Because most cases of RDS are self-limited, the goal of treatment is to minimize abnormal physiologic variations and superimposed iatrogenic problems. Treatment of infants with RDS is best carried out in the NICU.

Continuous monitoring of vital signs, review of chest radiography, and monitoring of blood gas values guides therapy in RDS. Oxygenation (So_2) should be assessed by continuous pulse oximetry. Capillary blood samples are of limited value for determining Po_2 but may be useful for Pco_2 and pH monitoring. Arterial blood gas samples provide the most accurate assessment of oxygenation. Monitoring of blood gas parameters and mean arterial blood pressure through an umbilical or peripheral arterial catheter is useful in managing the shocklike state that may occur during the initial hours in premature infants who have been asphyxiated or have severe RDS. Because of the difficulty in distinguishing group B streptococcal or other bacterial infections from RDS, empirical antibiotic therapy should be indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested, although the choice of antibiotics should be based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated (see Chapter 129).

Nasal Continuous Positive Airway Pressure

Warm, humidified oxygen should be provided at a concentration sufficient to keep Pao_2 between 50 and 70 mm Hg (91–95% Sao_2) to maintain normal tissue oxygenation while minimizing the risk of O_2 toxicity. If there is significant respiratory distress (severe retractions and expiratory grunting) or if Sao_2 cannot be kept >90% at an Fio_2 of ≥40, applying nasal continuous positive airway pressure (nCPAP) at 5-8 cm H_2O is indicated and usually produces a rapid improvement in oxygenation. Nasal CPAP reduces collapse of surfactant-deficient alveoli and improves both FRC and ventilation-perfusion matching. Early use of nCPAP for stabilization of at-risk preterm infants beginning early (in the delivery room) reduces the need for mechanical ventilation. Alternatives to nCPAP include noninvasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC). NIPPV is generally unsynchronized, but intermittent higher pressures do appear to improve oxygenation and ventilation over several hours. Additionally, NIPPV may limit apnea as a cause of respiratory failure. **HFNC** used heated and humidified oxygen flow generally upward of 2 L/min to provide distending pressures to the airways. The distending pressure is variable, which may contribute to HFNC failure. The amount of nCPAP required usually decreases after approximately 72 hours of age, and most infants can be weaned from nCPAP shortly thereafter.

Surfactant Replacement Therapy

Surfactant deficiency is the primary pathophysiology of RDS. Immediate effects of surfactant replacement therapy include improved alveolar-arterial oxygen gradients, reduced ventilatory support, increased pulmonary compliance, and improved chest radiograph appearance. In the past, *intratracheal* surfactant replacement for symptomatic premature infants immediately after birth (prophylactic) or during the first few hours of life *(early rescue)* showed reduced air leak and mortality from RDS. However, substantial evidence supports the feasibility and efficacy of **nCPAP** as the *primary* means of respiratory support for preterm infants with RDS with addition of surfactant based on clinical indication. Nasal CPAP started at birth is as effective as prophylactic or early surfactant and is associated with a reduction in bronchopulmonary dysplasia (BPD). *Nasal CPAP is therefore the approach of choice for the delivery room management of a preterm neonate at risk for RDS.*

In neonates with RDS who fail nCPAP and require intubation and mechanical ventilation, treatment with endotracheal surfactant should be initiated immediately to avoid lung injury. *Assisted ventilation and surfactant are indicated for infants with RDS who cannot keep oxygen saturation >90% while breathing 40% oxygen and receiving nCPAP.* Delays in delivering surfactant once clinical criteria are met is associated with poorer outcomes including increased mortality, increased incidence of **pulmonary air leak,** and increased risk for **BPD**. Repeated dosing is given every 6-12 hours for a total of two to four doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management. Additional required on-site staff support includes nurses and respiratory therapists experienced in the ventilatory management of preterm infants. Bolus delivery of surfactant is generally associated with better distribution throughout the lungs and faster improvement. Lung recruitment strategies include modest increase in tidal volume or positive end-expiratory pressure (PEEP) before surfactant administration, which may improve distribution. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Complications of surfactant replacement therapy include transient hypoxia, hypercapnia, bradycardia and hypotension, blockage of endotracheal tube (ETT), and pulmonary hemorrhage.

A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. There do not appear to be significant, consistent benefits to one preparation over another. Infants requiring ventilator support after 1 week of age may experience transient episodes of surfactant dysfunction temporally associated with episodes of infection and respiratory deterioration. Surfactant treatment may be beneficial in these infants.

Recognizing the benefits of surfactant replacement therapy, in addition to the potential protective effects of prophylactic nCPAP, some experts recommend intubation for prophylactic or early rescue surfactant replacement therapy, followed by extubation back to nCPAP immediately once the infant is stable (usually within minutes). This method is commonly referred to *as intubate, surfactant, and extubate (INSURE).* A variation of the INSURE method has evolved known as *MIST (minimally invasive surfactant therapy)* or *LISA (less invasive surfactant administration),* in which a small feeding tube, rather than an ETT, is used to deliver intratracheal surfactant to a spontaneously breathing infant on nCPAP. LISA and/or MIST are increasingly being utilized as the preferred method for delivering surfactant in infants who are not anticipated to require prolonged invasive ventilation. The combination of LISA, antenatal corticosteroids, nCPAP, and limitation of positive pressure ventilation in the delivery room was associated with decreased rates of BPD when compared to INSURE. Other methods of surfactant delivery are under investigation including the use of laryngeal mask airway and the use of nebulized surfactant to avoid airway manipulation altogether. In two studies of aerosolized surfactant, the need for intubation was reduced by ~50%.

Mechanical Ventilation

Infants with respiratory failure or persistent apnea require assisted mechanical ventilation. Strict definitions for respiratory failure in extremely preterm infants with RDS are not agreed on universally, but reasonable measures of respiratory failure are (1) arterial blood pH <7.20, (2) $Paco_2$ ≥60 mm Hg, (3) Sao_2 <90% at O_2 concentration of 40% *and* nCPAP of 5-8 cm H_2O, and (4) persistent or severe apnea. The goal of mechanical ventilation is to improve oxygenation and ventilation without causing pulmonary injury or oxygen toxicity. Acceptable ranges of arterial blood gas (ABG) values vary significantly among institutions but generally range from Pao_2 50-70 mm Hg (Spo_2 >90%), $Paco_2$ 45-65 mm Hg (and higher after the first few days when risk of IVH is less), and pH 7.20-7.35. During mechanical ventilation, **oxygenation** is improved by increasing either Fio_2 or the mean airway pressure. The mean airway pressure can be increased by raising the peak inspiratory pressure (PIP), inspiratory time, ventilator rate, or PEEP. Adjustment in PEEP is usually most effective; however, excessive PEEP may impede venous return, thereby reducing cardiac output and O_2 delivery (see Chapter 89.1). PEEP levels of 4-6 cm H_2O are usually safe and effective and assist in establishing FRC. **CO_2 elimination** is determined by the minute ventilation, which is a product of the tidal volume (dependent on the inspiratory time and PIP) and ventilator rate. Ventilator settings typically include a tidal volume of 4-6 mL/kg and a starting rate of approximately 40 breaths/min. With use of high ventilatory rates, relatively short inspiratory time and sufficient expiratory time should be allowed to avoid air trapping and inadvertent PEEP.

Synchronized intermittent mechanical ventilation (SIMV) delivered by time-cycled pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. With **pressure-limited** SIMV, a set PIP is delivered in synchrony with the patient's own breaths for a specified rate per minute. For breaths above the set rate, pressure support breaths (8-10 cm H_2O above PEEP) are provided to help overcome the resistance associated with spontaneous breathing through the ETT. In pressure-limited ventilation, the delivered tidal volume is directly proportional to the respiratory compliance. Rapid changes in compliance occur with surfactant replacement therapy, requiring careful attention to tidal volumes and appropriate adjustments in PIP. In **volume-targeted** ventilation a specific tidal volume is set, and the PIP required to deliver it varies inversely with the respiratory compliance. Studies indicate that lung damage is related to recurrent lung collapse and overdistension rather than high pressures, thus volume-targeted ventilation may represent the most lung protective strategy of conventional ventilation. Evidence suggests that volume-targeted ventilation results in fewer pulmonary air leaks and may improve survival without BPD.

Neurally adjusted ventilatory assist (NAVA) is a ventilator strategy that integrates electrical signals from the diaphragm to synchronize ventilator breaths with the patient. Increased diaphragmatic electrical signal indicates the impending onset of a breath. The strength of electrical signal indicates the size of breath intended by the patient. Using this strategy, the timing and tidal volume can be customized to the patient on a breath-by-breath basis, and this is believed to decrease overall pressures required and limit lung damage. NAVA technology can also be used to synchronize noninvasive ventilation. To date there is insufficient evidence to compare the outcomes of infants with RDS initially managed on NAVA ventilation to those managed with pressure-limited or volume-limited SIMV.

High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min or 5-20 Hz). This ventilation strategy maintains sustained alveolar expansion and therefore limits injury associated with recurrent atelectasis. HFV may improve elimination of CO_2 and improve oxygenation in patients who show no response to conventional ventilators, as well as those who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) are the most frequently used methods. There is not strong evidence to favor HFOV over HFJV or vice versa. Many investigators have examined the use of HFV as a primary mode of ventilation in infants with RDS. There is some evidence that HFV may result in decreased rates of BPD and pulmonary air leak when compared to pressure-limited SIMV; however, superiority over volume-targeted SIMV has not been consistently demonstrated.

Permissive Hypercapnia and Avoidance of Hyperoxia

Permissive hypercapnia is a strategy for management of patients receiving ventilatory support in whom priority is given to limiting ventilator-associated lung injury by tolerating relatively high levels of $Paco_2$ (>60-70 mm Hg). Permissive hypercapnia can be implemented during nCPAP and mechanical ventilation but has not been shown to significantly impact outcomes. Hypocarbia is associated with poorer outcomes; therefore careful monitoring of Pco_2 should be undertaken and moderate hypercapnia (>40-50 mmHg) can be tolerated. Hyperoxia may also contribute to lung injury in preterm infants. However, a lower target range of oxygenation (85–89%) compared with a higher range (91–95%) increases mortality and does not alter rates of BPD, BPD/death, blindness, or neurodevelopmental impairment. Therefore the currently recommended range of oxygen saturation targets is 91–95%.

Discontinuation of Mechanical Ventilation

Strategies for weaning infants from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes. Extubation to nCPAP prevents postextubation atelectasis and reduces the need for reintubation. NIPPV may further decrease the need for reintubation in premature infants, particularly when combined with NAVA technology to allow synchronization. HFNC (1-8 L/min) oxygen is often used to support term and near-term infants following extubation and appears to be comparable to nCPAP in preventing postextubation failure. It is not clear whether nCPAP, NIPPV, or HFNC is more efficacious for promoting normal lung development and preventing BPD, but there is more evidence associated with nCPAP in extremely preterm infants. Preloading with methylxanthines enhances the success of extubation.

Other Pharmacologic Therapies

There are no pharmacologic therapies superior or equal to the efficacy of maintaining FRC (through noninvasive respiratory support and mechanical ventilation when necessary) and providing surfactant replacement therapy in the treatment of RDS. Systemic corticosteroids (predominantly dexamethasone), although effective in improving respiratory mechanics and reducing the incidence of BPD and death, are associated with increased risk of cerebral palsy and neurodevelopmental impairment when used indiscriminately (see Chapter 127).

Inhaled nitric oxide (iNO) has been evaluated in preterm infants following the observation of its effectiveness in term and near-term infants with hypoxemic respiratory failure. Although iNO improves oxygenation in term and near-term infants with hypoxic respiratory failure or persistent pulmonary hypertension of the neonate, trials in preterm infants have not shown significant benefit.

PROGNOSIS

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal corticosteroids, postnatal surfactant use, and improved modes of ventilation have resulted in low mortality from RDS (approximately 10%). Mortality increases with decreasing GA. Optimal results depend on the availability of experienced and skilled personnel, care in specially designed and organized regional hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irremediable congenital malformation. Premature infants with RDS may go on to develop chronic lung disease and ultimately BPD (see Chapter 127).

Pulmonary air leaks (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema) are observed in 3–9% of extremely preterm infants with RDS (see Chapter 132). PPV with excessive

inspiratory pressures (and therefore excessive tidal volumes), either during resuscitation at delivery or in the initial hours of mechanical ventilation, is a common risk factor, but air leaks can also occur in infants breathing spontaneously. Although the risk of air leak was increased in infants receiving a higher level of nCPAP (up to 8 cm H_2O) in the CPAP or Intubation at Birth (COIN) trial, subsequent trials have not demonstrated a similar effect.

Additional complications of RDS may result from intubation procedures during the treatment of this disorder. Airway injury may occur at the time of intubation and adequate training is essential. Complications of intubation including ventilator-associated pneumonias and transient obstruction of the artificial airway are possible. With prolonged or recurrent intubation local pressure injury can lead to the development of subglottic stenosis.

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126.1 Patent Ductus Arteriosus

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

INCIDENCE AND PATHOPHYSIOLOGY

The ductus arteriosus is a fetal vascular shunt connecting the aorta to the pulmonary artery that allows oxygenated blood to bypass the uninflated fetal lungs and enter the systemic circulation. Following term birth, the ductus arteriosus constricts and is usually closed in the first few days of life. Although ductal closure occurs by 72 hours after birth in almost all term infants, the ductus remains patent in 65% of preterm infants born at <30 weeks' GA and in 85% of infants born at 24 weeks' GA. Risk factors for delayed closure of the PDA include hypoxia, acidosis, increased pulmonary pressure secondary to pulmonary vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins (which dilate the ductus). Shunting through the patent ductus arteriosus (PDA) may initially be bidirectional or right to left. As RDS resolves, PVR decreases, and predominantly left-to-right shunting may occur, leading to left ventricular (LV) volume overload and pulmonary edema.

CLINICAL MANIFESTATIONS

Manifestations of PDA may include (1) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a machine-like continuous or systolic murmur; (2) radiographic evidence of cardiomegaly and increased pulmonary vascular markings; (3) hepatomegaly; (4) increasing oxygen dependence; (5) carbon dioxide retention; and (6) less often renal failure. Infants with a hemodynamically significant PDA often require escalation of ventilator and oxygen support. The diagnosis is confirmed by echocardiographic visualization of a PDA with Doppler flow imaging that demonstrates left-to-right shunting. A hemodynamically significant PDA by echocardiogram has a PDA ≥1.5 mm, unrestricted pulsatile transductal flow, left atrial to aortic root ratio ≥1.5, and absent (end) diastolic flow in the descending aorta (Table 126.1).

TREATMENT

Interventions to encourage ductal closure include fluid restriction, cyclooxygenase (COX) inhibitors (indomethacin or ibuprofen), acetaminophen, and surgical ligation. Short-term benefits of any therapy must be balanced against adverse effects, such as transient renal dysfunction and fluid imbalances associated with indomethacin.

By the time of discharge in the majority of extremely preterm infants (>90%), the PDA will close spontaneously. Spontaneous ductal closure may be facilitated by general supportive measures, including early (<7 days of age) avoidance of excessive fluid administration and judicious use of diuretics to manage pulmonary edema. However, within the first week of life, in 30% of infants with birthweight <1,500 g and 70% of infants <1,000 g, the PDA persists. Although many preterm infants with persistent PDA will remain clinically stable while awaiting spontaneous closure, approximately 60% of infants <1,000 g will develop significant clinical instability (hypotension, renal failure, worsening respiratory failure secondary to pulmonary edema). Pharmacologic and surgical ductal closure may be indicated in the premature infant with a moderate to large, hemodynamically significant PDA when there is a delay in clinical improvement or deterioration.

Table 126.1 Summary of Essential Parameters Used for Echocardiographic Assessment and Hemodynamic Evaluation of PDA

PDA EVALUATION CRITERIA	ESSENTIAL ECHOCARDIOGRAPHIC PARAMETERS FOR ASSESSMENT OF PDA AND HEMODYNAMIC EVALUATION
Ductal characteristics	PDA size (small 2 mm) and flow direction (left to right, right to left, or bidirectional) and Doppler assessment with maximum velocity (Vmax) in systole and end-diastole
Assessment of pulmonary over circulation	Dilated left side of the heart on visual inspection "eyeballing" and LA/Ao ratio (mild 1.6) OR LVEDD (correlate with *z* scores) OR LPA diastolic velocity, mean velocity >0.42 m/sec, end-diastolic velocity >0.2 m/sec OR reversal of mitral E/A ratio *Document presence or absence and magnitude of intraatrial shunt
Assessment of systemic hypoperfusion	Retrograde or absent blood flow during diastole in descending aorta OR celiac trunk or SMA OR anterior or middle cerebral artery

A comprehensive echocardiographic assessment should be performed to rule out any underlying congenital heart defect or pulmonary hypertension and delineate orientation of arch (left or right sidedness) before any intervention to close the PDA.
E/A ratio, ratio of the early (E) to late (A) ventricular filling velocities; LA/Ao, left atrial to aortic ratio; LPA, left pulmonary artery; LVEDD, left ventricular end-diastolic diameter; PDA, patent ductus arteriosus; SMA, superior mesenteric artery.
From Singh Y, Fraisse A, Erdeve O, Atasay B. Echocardiographic diagnosis and hemodynamic evaluation of patent ductus arteriosus in extremely low gestational age newborn (ELGAN) infants. *Front Pediatr.* 2020;8:Article 573627. Table 1.

Pharmacologic Closure

Pharmacologic closure of the PDA has been described using COX inhibitors that inhibit prostaglandin production, with equivalent efficacy and safety profiles described for ibuprofen and indomethacin. The efficacy of pharmacologic *therapy* is inversely proportional to the gestational and postnatal age, and closure is more likely when medication is administered before 21 days of age. However, successful closure has been reported up to 8 weeks of age. Whether indomethacin or ibuprofen is used, 20–40% of infants demonstrate treatment failure, and of those infants, 10–20% require eventual surgical ligation. Rates of recurrence following successful pharmacologic closure in general are low (<15%). Neither therapy significantly impacts the rate of NEC, BPD, or mortality. **General contraindications** to both indomethacin and ibuprofen include thrombocytopenia (<50,000 platelets/mm^3), active hemorrhage (including severe IVH), NEC or isolated intestinal perforation, elevated plasma creatinine (>1.8 mg/dL), or oliguria (urine output <1 mL/kg/hr). Importantly, the concomitant use of hydrocortisone and indomethacin in extremely preterm infants must be avoided because the combination is associated with a dramatic increase in spontaneous intestinal perforation. Although indomethacin reduces

mesenteric blood flow, mounting experience suggests that low-volume trophic enteral feeding during administration is safe.

Prophylactic **indomethacin** given over the first 72 hours of age to preterm infants with birthweight <1,000 g reduces the incidence of severe IVH (grade III/IV), pulmonary hemorrhage, symptomatic PDA, and need for surgical PDA ligation. Although often implicated in spontaneous intestinal perforation and NEC, randomized controlled trials (RCTs) have failed to demonstrate that indomethacin increases their risk significantly. Short-term side effects include reductions in cerebral, mesenteric, and renal blood flow. Oliguria unresponsive to diuretic therapy is observed frequently. Dosing regimens for indomethacin vary considerably, but it usually is administered as a slow IV infusion (0.1-0.2 mg/kg/dose over 30 minutes) every 12-24 hours for three doses. A repeat course can be attempted if the duct fails to close or reopens, but additional (>2) courses do not appear to be efficacious. Longer courses (5-7 days) of indomethacin are not recommended because of to an increased risk of NEC in one trial.

Ibuprofen is as effective as indomethacin in closing a PDA, but ibuprofen is associated with reduced rates of oliguria and a small but significant reduction in the length of mechanical ventilation. Although higher doses may improve closure rates in the most immature infants, the typical IV or enteral dosing regimen for ibuprofen is 10 mg/kg for one dose, followed by two doses of 5 mg/kg every 24 hours. A meta-analysis showed that a higher dose of oral ibuprofen using 20 mg/kg per dose for one dose, followed by 10 mg/kg per dose for two doses 24 hours apart is superior in closing the PDA compared to indomethacin or the traditional ibuprofen dosing. As with indomethacin, a repeat course may be considered, but additional courses of ibuprofen are not efficacious and not recommended. Risk of NEC is *not increased* with indomethacin, but in comparison, ibuprofen *reduces* the relative risk of NEC. Unlike indomethacin, ibuprofen has not been shown to reduce the risk of severe IVH. Compared to the IV route, enteral ibuprofen may be more efficacious. Whether ibuprofen used in combination with hydrocortisone results in increased risk of spontaneous intestinal perforation is unknown.

Oral acetaminophen has been shown to be an effective medication in closing the PDA, with fewer side effects than existing agents. It is given enterally at 15 mg/kg per dose q6h for 3 days. In practice, most clinicians will use a course of one of the previously mentioned medications as first-line therapy (typically ibuprofen) and follow with a second course of acetaminophen in a few days if the PDA remains patent and symptomatic.

Surgical Ligation

The infant whose *symptomatic* PDA fails to close with pharmacologic interventions or who has contraindications to COX inhibitors is a candidate for surgical closure via an open thoracotomy. Although the long-term benefits are unclear, surgical ligation in infants born at <28 weeks' GA and <1,250 g is associated with improved survival. Surgical mortality is very low even in extremely low birthweight (ELBW) infants. However, **postligation cardiac syndrome**, a significant drop in blood pressure 6-12 hours after ductal ligation, is experienced by up to 50% of low birthweight (LBW) infants. The hypotension has been attributed to increased systemic vascular resistance along with decreased pulmonary venous return, resulting in impaired preload and LV function. Fluid resuscitation, inotropic support (with dobutamine or milrinone), and hydrocortisone are usually effective. Other complications of surgery include hemorrhage, pneumothorax, chylothorax, Horner syndrome, and injury to the recurrent laryngeal nerve resulting in vocal cord dysfunction. Inadvertent ligation of the left pulmonary artery or the transverse aortic arch has rarely been reported. Increased rates of neurodevelopmental impairment have been reported following surgical ligation, although a causal relationship remains uncertain. Due to the complications associated with surgical ligation, many centers have moved away from this modality and use a less invasive, percutaneous approach to PDA closure.

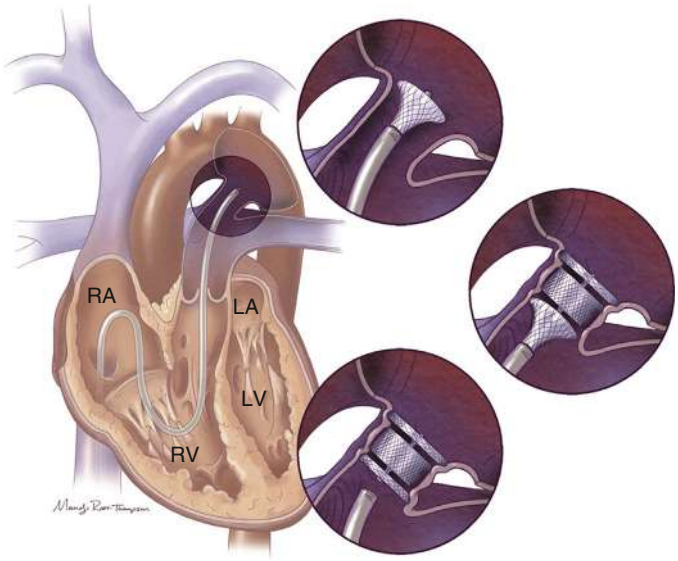

Fig. 126.7 Percutaneous device closure of a PDA using the Amplatzer Piccolo Occluder. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *(From Backes CH, Giesinger RE, Rivera BK, et al. Percutaneous closure of the patent ductus arteriosus in very low weight infants: considerations following US Food and Drug Administration approval of a novel device. J Pediatr. 2019;213:218–221.)*

Percutaneous Closure of the Patent Ductus Arteriosus

Percutaneous closure of the PDA is a safe and effective procedure for definitive PDA closure. In 2019, the U.S. Food and Drug Administration approved the Amplatzer PiccoloOccluder (Abbott Diagnostics, North Chicago, IL) for percutaneous PDA closure in preterm infants weighing 700 g or more (Fig. 126.7). A trial in 100 infants weighing <2 kg showed that this technique of PDA closure is 99% effective with a 2% risk of adverse events. Although a comparative trial has not been done against the traditional surgical approach, most US centers use percutaneous closure as the first-line approach for PDA closure when conservative treatment fails. This procedure is done under cardiac anesthesia in the catheterization laboratory. The femoral vein is accessed using modified Seldinger technique, and then, under fluoroscopic guidance, a catheter is advanced through the femoral vein all through the right ventricular and across the PDA and the Piccolo device is placed. This technique permits injection of contrast before and after device placement to ensure appropriate device selection, measure size of the PDA, and ensure that there is no occlusion of the descending aorta or left pulmonary artery after device placement. If there is evidence of narrowing, the device can be recaptured and repositioned until a satisfactory result is obtained. Rarely, appropriate device placement is not achieved, and the patient may have to undergo surgical ligation. The short-term complications are bleeding at the insertion site, embolization of the device into the descending aorta or left pulmonary artery, post-PDA ligation syndrome, and residual shunting across PDA. The long-term complications are unknown, but these patients likely need surveillance echocardiography until 2-3 years of age.

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Chapter 127

Bronchopulmonary Dysplasia

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

INCIDENCE

Bronchopulmonary dysplasia (BPD; also known as *chronic lung disease of prematurity*) is a clinical pulmonary syndrome that develops in the majority of extremely preterm infants and is defined by a prolonged need for respiratory support and supplemental oxygen. Almost 60% of infants born at ≤28 weeks' gestation will develop BPD, and the incidence of BPD increases inversely with gestational age. For infants born at 22-24 weeks, essentially 100% will develop BPD, the majority of whom will have moderate to severe disease. As neonatal care has improved and use of antenatal corticosteroids has become the standard of care, survival of infants born at the extreme of viability has improved, and BPD is encountered with increased prevalence. In the United States, an additional 10,000-15,000 new cases occur annually. Despite decades of experience, the incidence of BPD remains largely unchanged.

ETIOLOGY AND PATHOPHYSIOLOGY

BPD develops following preterm birth and the necessary life-supporting interventions (particularly mechanical ventilation and supplemental oxygen) that cause neonatal lung injury. As very low birthweight (VLBW) infant's survival has improved by advances in neonatal care, the clinical syndrome associated with BPD has evolved. The clinical, radiographic, and lung histology of classic BPD described in 1967 by Northway, before widespread use of antenatal corticosteroids and postnatal surfactant, was that of a disease of preterm infants who were more mature. Infants who developed BPD initially demonstrated classic respiratory distress syndrome (RDS), but the injurious mechanical ventilation and excessive supplemental oxygen required to support them resulted in a progressive, severe fibroproliferative lung disease. Improvements in respiratory care, as well as the introduction of surfactant and antenatal steroids, have allowed for less aggressive respiratory support strategies, and the need for excessive ventilator support and high percentages of inspired supplemental oxygen has decreased.

Despite a reduction in the fibroproliferative disease described previously, infants born in the modern era of neonatal care continued to require supplemental oxygen for prolonged periods. The *new* BPD is a disease primarily of infants with birthweight <1,000 g who were born at <28 weeks' gestation, some of whom have initially little or no lung disease at birth but over the first weeks of age experience progressive respiratory failure. Infants with the new BPD are born at a more immature stage of distal lung development, and lung histology demonstrates variable saccular wall fibrosis, minimal airway disease, abnormal pulmonary microvasculature development, and alveolar simplification. Although the etiology remains incompletely understood, the histopathology of BPD indicates interference with normal alveolar septation and microvascular maturation.

The pathogenesis of BPD is likely multifactorial, but pulmonary inflammation and lung injury in an immature lung are consistently observed. Alveolar collapse **(atelectrauma)** as a consequence of surfactant deficiency, together with ventilator-induced phasic overdistention of the lung **(volutrauma)**, promotes lung inflammation and injury. Supplemental oxygen produces free radicals that cannot be metabolized by the immature antioxidant systems of VLBW neonates and further contributes to the injury. Pulmonary inflammation evidenced by infiltration of neutrophils and macrophages in alveolar fluid, as well as a host of proinflammatory cytokines, contributes to the progression of lung injury. Pre- and postnatal infection, excessive pulmonary blood flow via the patent ductus arteriosus (PDA), excessive administration of intravenous fluid, and pre- and postnatal growth failure are also significantly associated with the development of BPD. In addition, pulmonary artery hypertension may complicate BPD. Although the mechanisms are unclear, all likely promote lung injury by necessitating increased or prolonged respiratory support or interfering with lung repair. Regardless, the result is an interference with normal development of the alveolar-capillary unit and interference with normal gas exchange.

CLINICAL MANIFESTATIONS

Over the first several weeks of age, infants developing BPD demonstrate persistent, often progressive respiratory distress and the need for respiratory support and supplemental oxygen. In extremely low birthweight (ELBW) infants at risk for BPD, the need for supplemental oxygen over the first 2 weeks of age follows one of three distinct patterns. Infants that follow the natural course of RDS, and by 3-4 days of age require minimal (F_{IO_2} <0.25) supplemental oxygen, have a low (<20%) risk of developing BPD. Infants who initially have a low O_2 requirement (F_{IO_2} <0.25) during the first week, but then experience early pulmonary deterioration and increased O_2 requirement (F_{IO_2} >0.25) during the second week, have a modest risk (approximately 50%) of developing BPD. Infants that have an early, persistently high (F_{IO_2} >0.25) need for supplemental oxygen have a significantly high (70%) risk of developing BPD.

Respiratory distress, commonly characterized by tachypnea and retractions, persists or worsens and is associated with hypercapnia, hypoxia, and oxygen dependence. The chest radiograph evolves from that of RDS to relative hyperinflation and fine, diffuse interstitial opacities. Wandering atelectasis is common. In the most severe cases, usually associated with prolonged mechanical ventilation and chronically high supplemental oxygen needs, frank cystic changes and/or pneumatoceles are observed (Fig. 127.1). Infants with severe BPD receiving invasive ventilation often demonstrate airway obstruction. Excessive airway mucus and edema, airway instability caused by acquired tracheobronchomalacia, and bronchospasm are proposed etiologies. Acute airway obstruction is manifest clinically by abrupt hypoxemia and bradycardia and is often referred to as *BPD spells*. Acute, intermittent right-to-left intracardiac or intrapulmonary shunting caused by abrupt elevations in pulmonary artery pressure (PAP) may also contribute and resemble BPD spells. Spells are notoriously difficult to control, but occasionally will respond to bronchodilators, increasing positive end-expiratory pressure (PEEP), and sedation acutely.

A common complication of BPD is **pulmonary hypertension**. Prospective surveillance indicates that in approximately 15% of all infants born at <1,000 g and <28 weeks' gestational age, echocardiographic signs of pulmonary hypertension will develop. Prenatal growth restriction, prolonged duration of mechanical ventilation and supplemental oxygen, and increasing severity of BPD are all associated with an increased risk. Pulmonary hypertension has been reported in as many as 40% of infants with the most severe BPD and can progress to right-sided heart failure. Pulmonary hypertension complicating BPD has been associated with increased mortality.

DIAGNOSIS

BPD is diagnosed when a preterm infant requires supplemental oxygen for the first 28 postnatal days; it is further classified at 36 weeks' postmenstrual age (PMA) according to the degree of O_2 supplementation (Table 127.1). Neonates receiving positive pressure support or ≥30% supplemental O_2 at 36 weeks' PMA or at discharge (whichever occurs first) are diagnosed as having **severe** BPD; those requiring <30% supplemental O_2 have **moderate** BPD; and those who previously required O_2 supplementation for at least 28 days but are currently breathing room air have **mild** BPD. Infants who require oxygen for <28 days of life have "no BPD." Infants receiving supplemental O_2 should undergo a stepwise reduction in supplemental O_2 to room air at 36 weeks while under continuous observation and with Spo_2 monitoring to determine whether they can be weaned off oxygen

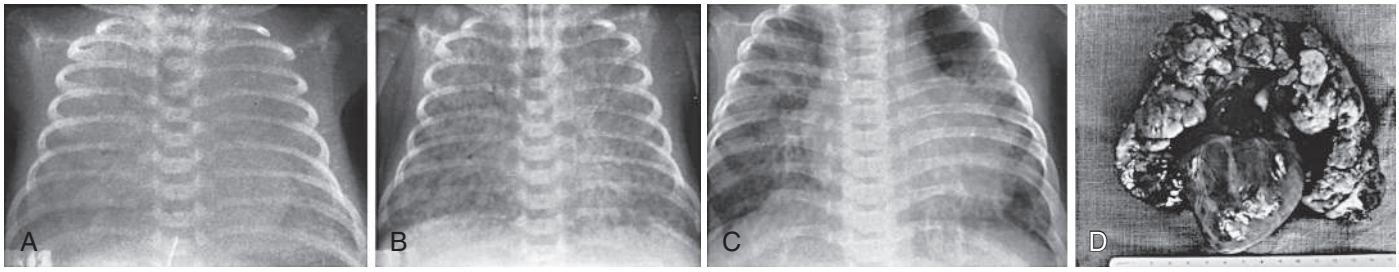

Fig. 127.1 Pulmonary changes in infants treated with prolonged, intermittent positive pressure breathing with air containing 80–100% oxygen in the immediate postnatal period for the clinical syndrome of hyaline membrane disease. **A,** A 5-day-old infant with nearly complete opacification of the lungs. **B,** A 13-day-old infant with "bubbly lungs" simulating the radiographic appearance of the Wilson-Mikity syndrome. **C,** A 7-month-old infant with irregular, dense strands in both lungs, hyperinflation, and cardiomegaly suggestive of chronic lung disease. **D,** Large right ventricle and a cobbly, irregular aerated lung of an infant who died at 11 months of age. This infant also had a patent ductus arteriosus. *(From Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. N Engl J Med. 1967;276:357–368.)*

Table 127.1 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria*

	GESTATIONAL AGE	
	<32 Wk	**≥32 Wk**
Time point of assessment	36 wk PMA or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**:	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**:
Mild BPD	Breathing room air at 36 wk PMA or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need† for <30% oxygen at 36 wk PMA or discharge home, whichever comes first	Need† for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need† for ≥30% oxygen and/or positive pressure (PPV or nCPAP) at 36 wk PMA or discharge home, whichever comes first	Need† for ≥30% oxygen and/or positive pressure (PPV or nCPAP) at 56 days postnatal age or discharge home, whichever comes first

*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most frequently respiratory distress syndrome (RDS). Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for >12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk PMA or at 56 days postnatal age or discharge should not reflect an "acute" event; rather, it should reflect the infant's usual daily therapy for several days preceding and after 36 wk PMA, 56 days postnatal age, or discharge.

†A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD, Bronchopulmonary dysplasia; nCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.

From Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 2001;163:1723–1729.

(physiologic definition of BPD). This test is highly reliable and correlated with discharge home on oxygen, length of hospital stay, and hospital readmissions in the first year of life. The risk of neurodevelopmental impairment and pulmonary morbidity and the severity of BPD are directly correlated.

Despite its simplicity, the current severity-based definition of BPD has limitations. Because of incomplete or inaccurate data related to hospital transfer or early discharge, in a significant number of infants the diagnosis of BPD is either not documented or misapplied. Additionally, those infants requiring O_2 support at relatively high flow (>2 L/min) or very low (<0.25 L/min) or those receiving other modes of noninvasive ventilation are not well characterized. Calculation of *effective oxygen* may be helpful but is cumbersome and not well validated. Clinical trials have relied on the need for supplemental O_2 at 36 weeks PMA to define BPD. Although this definition can diagnose BPD in the highest percentage of infants, it cannot discriminate between infants with milder BPD from those with most severe forms of BPD. A National Institute of Child Health and Human Development (NICHD) workshop on BPD developed a definition of BPD that would address some of the concerns mentioned earlier (Table 127.2). Specifically, it incorporates the diverse forms of respiratory support used, distinguishes infants who are receiving invasive vs noninvasive positive pressure ventilation (PPV), and introduces the term "lethal BPD" or grade III(A) severe BPD to identify infants who die from this disease before 36 weeks' PMA.

PREVENTION

In general, there remains a lack of effective interventions that prevent BPD. Avoidance of mechanical ventilation with the early use of nCPAP and early, selective surfactant replacement therapy with rapid extubation decrease the incidence of BPD modestly. The avoidance of mechanical ventilation achieved by the combination of early rescue surfactant by the INSURE, MIST, or LISA method with nasal continuous positive airway pressure (nCPAP) has been associated with a modest reduction in BPD (see Chapter 126). Gentle ventilation strategies, including volume-targeted ventilation and high-frequency oscillatory ventilation (HFOV), have also been associated with small, inconsistent reductions in BPD. Caffeine therapy for apnea of prematurity has also been associated with a decreased risk of BPD. Although the mechanisms are unknown, caffeine likely supports effective spontaneous respiration and decreases the likelihood that an infant will need invasive mechanical ventilation.

Table 127.2 New Definition of Bronchopulmonary Dysplasia Based on the 2016 NICHD Executive Workshop on Bronchopulmonary Dysplasia

For infants born <32 wk gestation, with radiographic evidence of parenchymal lung disease, who at 36 wk require one of the following F_{IO_2}/oxygen levels/oxygen concentrations for ≥3 consecutive days to maintain Sp_{O_2} in the 90–95% range

	INVASIVE IPPV	nCPAP, NIPPV, OR NASAL CANNULA ≥3 L/MIN	NASAL CANNULA 1-3 L/MIN	NASAL CANNULA <1 L/MIN
Grade I BPD	No	21% F_{IO_2}	22–29% F_{IO_2}	22–70% F_{IO_2}
Grade II BPD	21% F_{IO_2}	22–29% F_{IO_2}	≥30% F_{IO_2}	≥70% F_{IO_2}
Grade III BPD	>21% F_{IO_2}	≥30% F_{IO_2}		
Grade III(A) BPD	Infants who die between 14 days to 36 wk PMA from respiratory failure secondary to severe parenchymal lung disease not attributable to other neonatal morbidities			

NICHD, National Institute of Child Health and Human Development; BPD, bronchopulmonary dysplasia; IPPV, invasive positive pressure ventilation; nCPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation.
Adapted from Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr*. 2018;197:300–308.

Systemic corticosteroids (dexamethasone) given either early (<7 days of age to ventilated infants at risk of BPD) or late (>7 days of age to infants with progressing lung disease) prevent both mortality and BPD significantly, but because of the increased risk of cerebral palsy (CP) and neurodevelopmental impairment, their routine use is not recommended. The risk of neurodevelopmental impairment related to systemic corticosteroid use may be offset by the risk associated with BPD. A systematic review suggested that systemic corticosteroid therapy, when directed to infants with a ≥65% risk of developing BPD, may actually reduce the risk of neurodevelopmental impairment and CP. Although predictive models that use clinical characteristics have been described with promising accuracy, randomized trials using them to guide corticosteroid therapy have not been performed.

Inhaled corticosteroids administered to VLBW infants requiring mechanical ventilation at 7-14 days of age did not prevent BPD significantly. However, early, prolonged administration to mechanically ventilated extremely preterm infants until they no longer require oxygen or positive pressure support has been shown to reduce the risk of BPD, but with a concerning trend toward increased mortality. Experience with local delivery of corticosteroids by spiking surfactant with budesonide is emerging, and early data suggest that endotracheal administration of corticosteroids may reduce pulmonary inflammation and the risk of BPD and death. However, additional evidence is needed before widespread use is implemented. The routine use of antibiotics, inhaled bronchodilators, or diuretics has not been shown to *prevent* BPD.

TREATMENT

Treatment of evolving and established BPD is supportive. The basic tenets of therapy should include appropriate support of ventilation and aggressive nutritional support to optimize linear growth and encourage normal lung repair and development. Available evidence suggests short-term benefits (improved pulmonary mechanics, modest reductions in respiratory support parameters) without an indication of impact on clinically relevant outcomes (survival, need for long-term respiratory support, recurrent hospitalization). Currently, available evidence does not support the routine use of any pharmacologic agents in infants with evolving or established BPD. Treatment decisions must weigh the perceived benefit against the potential harm.

Diuretics and Fluid Restriction

Infants with BPD often have excessive pulmonary interstitial fluid that compromises lung function and increases work of breathing. Diuretic therapy (usually with furosemide or chlorothiazide) has been associated with short-term, temporary improvements in pulmonary compliance and the ability to wean respiratory support. Furosemide (1 mg/kg/dose IV or 2 mg/kg/dose orally [PO] every 12-24 hours) has been demonstrated to decrease pulmonary interstitial edema and pulmonary vascular resistance (PVR), improve pulmonary function, and facilitate weaning from mechanical ventilation and oxygen. Adverse effects of long-term furosemide therapy are common and include hyponatremia, hypokalemia, alkalosis, azotemia, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Sodium and potassium chloride supplementation is often necessary. Thiazide diuretics (e.g., chlorothiazide, 5-10 mg/kg/dose every 12 hours) have been used as an alternative to avoid hypercalciuria, limit nephrocalcinosis, and preserve bone development. Although avoidance of excessive fluid administration in the first few weeks of age is associated with a reduced risk of BPD, there is no evidence that fluid restriction (130-140 mL/kg/day) in established BPD has any impact. Whether using diuretics or fluid restriction, careful attention to maintaining appropriate electrolyte levels as well as providing adequate caloric intake (often >120-130 kcal/kg/day) is paramount to avoid negatively impacting nutrition.

Bronchodilators

Inhaled bronchodilators improve lung mechanics by decreasing airway resistance. **Albuterol** is a specific β_2-agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation but can exacerbate bronchomalacia. Changes in pulmonary mechanics may last 4-6 hours. Hypertension and tachycardia are adverse effects. Ipratropium bromide is a muscarinic antagonist related to atropine, but the bronchodilator effect is more potent. Use of ipratropium bromide in BPD has been associated with improved pulmonary mechanics. Compared with either agent used alone, combined use of albuterol and ipratropium bromide may be more effective. Few adverse effects have been noted. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD, especially if they are ventilator dependent, is unclear.

Corticosteroids

Systemic corticosteroids have been used to treat evolving and established BPD. In mechanically ventilated infants, systemic corticosteroids improve pulmonary mechanics, allow weaning of ventilator support and supplemental O_2, and facilitate extubation. When given at >7 days of age, long-term benefits include a reduced need for O_2 at 36 weeks PMA, improved survival, and decreased need for home O_2. Short-term adverse effects include hyperglycemia, hypertension, and transient hypertrophic obstructive cardiomyopathy. Long-term adverse effects include osteopenia, severe retinopathy of

prematurity (ROP), abnormal neurologic examination, poor brain growth, neurodevelopmental impairment, and CP. A strategy that utilizes a low cumulative dose (0.89 mg/kg of dexamethasone given over 10-day taper) in preterm infants who remain ventilator dependent after 7 days of age (and therefore have a high risk of developing BPD) facilitates weaning of ventilator and oxygen support and promotes successful extubation without an impact on long-term outcomes, including the incidence of BPD or neurodevelopmental impairment. The controversy concerning the appropriate use of systemic corticosteroids to prevent and/or treat BPD is ongoing, and until additional evidence is available, their use remains limited to infants with severe respiratory failure (ventilator dependent at >7-14 days of age with significant respiratory and oxygen support needs) at high risk for imminent death.

Inhaled corticosteroids (budesonide, fluticasone, and beclomethasone) have been described as an alternative therapy in evolving or established BPD. Small randomized controlled trials (RCTs) and case reports in infants with established moderate to severe BPD have not shown a significant benefit for pulmonary mechanics or reduction in the need for ventilator or oxygen support. Inhaled fluticasone propionate (corticosteroid) combined with salmeterol (long-acting β_2-agonist) may be beneficial.

Pulmonary Vasodilators

Many infants with evolving or established moderate and severe BPD demonstrate increased PVR caused by pulmonary microvascular maldevelopment and abnormal vasoreactivity. In infants *with* BPD with pulmonary hypertension, acute exposure to even modest levels of hypoxemia can cause PAP to increase abruptly. Maintaining infants with established BPD and pulmonary hypertension at higher So_2 targets (92–96%) can lower PAP effectively. For infants in whom appropriate O_2 supplementation and support of ventilation are ineffective, the use of low-dose inhaled nitric oxide (iNO) may improve oxygenation anecdotally. Despite its frequent use, there is no evidence to support the use of iNO to improve lung function, cardiac function, or oxygenation in evolving BPD. Several case series have reported on the use of the phosphodiesterase-5 inhibitor sildenafil in treating pulmonary hypertension in established moderate to severe BPD. Despite its widespread use, no RCTs are evaluating the safety and efficacy of sildenafil in preterm infants with BPD. However, many experts would recommend a trial of low-dose sildenafil (1 mg/kg/dose every 8 hours) for infants with evidence of pulmonary hypertension and persistent respiratory instability despite appropriate oxygen and ventilator support.

Chronic Respiratory Support

Experience suggests that maintaining functional residual capacity (FRC) with appropriate positive pressure support (with noninvasive support whenever possible) promotes optimal lung growth and development. Provision of nCPAP until respiratory status improves and oxygen dependence resolves, with subsequent transition directly to room air, may be beneficial. Continuation of caffeine therapy may facilitate spontaneous breathing and weaning from support. Established severe BPD with cystic, heterogeneous lung disease often requires prolonged mechanical ventilation. A long inspiratory time is required to adequately ventilate diseased lung units, and appropriate expiratory time is required to allow exhalation. The use of a low rate (<20-30 breaths/min), long inspiratory time (≥0.6 seconds) strategy is usually required. To attain appropriate minute ventilation, larger tidal volumes (10-15 mL/kg) may be necessary. Higher PEEP (often >6-8 cm H_2O) may be needed to attain adequate expansion and minimize gas-trapping caused by dynamic airway collapse. Gradual weaning of ventilator settings should be attempted as the infant grows and lung disease improves, but the incidence of death or tracheostomy placement for chronic ventilation may be as high as 20%. By 2-3 years of age, the majority of infants who undergo tracheostomy for severe BPD are successfully liberated from mechanical ventilation.

PROGNOSIS

Compared with extremely preterm infants without BPD, infants with BPD have higher rates of neurodevelopmental impairment, lung diffusion impairment, wheezing and airflow obstruction, rehospitalization, and mortality. The risk of these complications increases with BPD severity. Infants with grade III BPD are most likely to either die or have long-term respiratory morbidity. Prolonged mechanical ventilation, intraventricular hemorrhage (IVH), pulmonary hypertension, cor pulmonale, and oxygen dependence beyond 1 year of life are poor prognostic signs. Mortality in infants with BPD ranges from 10–25% and is highest in infants who remain ventilator dependent for >6 months. Cardiorespiratory failure associated with cor pulmonale and acquired infection (respiratory syncytial virus [RSV]) are common causes of death. Infants are at risk for severe RSV infections and must receive prophylactic therapy (see Chapter 307).

Pulmonary function slowly improves in most survivors because of ongoing lung repair and the natural period of lung growth and alveolarization. *Rehospitalization* for impaired pulmonary function is most common during the first 3 years of life and is much more common in infants requiring respiratory support at discharge. The incidence of physician-diagnosed asthma, use of bronchodilators, and wheezing is elevated. Despite a gradual decrease in symptom frequency, persistence of respiratory symptoms and abnormal pulmonary function test results are measurable in children, adolescence, and young adults. Although not always clinically apparent, pulmonary function testing consistently reveals impaired exercise capacity, reduced pulmonary diffusing capacity, and persistent expiratory flow obstruction. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality. The ultimate long-term pulmonary health of survivors of BPD is unknown. As trajectories of developing lung function remain abnormal in survivors of BPD, concerns have been raised highlighting the potential for pulmonary emphysema, chronic obstructive pulmonary disease, and pulmonary vascular disease resulting in early debilitating lung dysfunction.

Other complications of BPD include growth failure, neurodevelopmental impairment, and parental stress, as well as sequelae of therapy, such as nephrolithiasis, osteopenia, and electrolyte imbalance. Airway problems such as vocal cord paralysis, subglottic stenosis, and tracheomalacia are common and may aggravate or cause pulmonary hypertension. Subglottic stenosis may require tracheotomy or an anterior cricoid split procedure to relieve upper airway obstruction. Cardiac complications of BPD include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and development of aortopulmonary collateral vessels, which, if large, may cause heart failure.

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Chapter 128

Transient Tachypnea of the Newborn

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

INCIDENCE

Transient tachypnea of the newborn (TTN) is a clinical syndrome of self-limited tachypnea associated with delayed clearance of fetal lung fluid. Although the actual incidence is likely underreported, it is estimated at 3-6 per 1,000 term infant births, making TTN the most common etiology of tachypnea in the newborn. Twin gestation, maternal asthma, maternal hypertension, late prematurity, precipitous delivery, perinatal depression, gestational diabetes, macrosomia, and cesarean delivery, particularly without labor, are common risk factors.

ETIOLOGY AND PATHOPHYSIOLOGY

TTN is believed to result from ineffective clearance of fetal lung fluid. Retained fetal lung fluid decreases pulmonary compliance and impedes gas exchange. Clearance of fetal lung fluid occurs through increased expression of epithelial sodium channels (ENaCs) and sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase) that drive active sodium (and thereby fluid) reabsorption. There is evidence that the channels involved in fluid clearance differ for infants with TTN. Additional lung fluid is cleared via compressive forces at the time of delivery and hydrostatic forces with the infant's first breaths (see Chapter 124.1). Decreased respiratory effort can delay fluid clearance and increase the risk for TTN.

CLINICAL MANIFESTATIONS

TTN is characterized by the early onset of tachypnea (>60 breaths/min), sometimes with retractions or expiratory grunting and occasionally with cyanosis that is relieved by minimal O_2 supplementation (<40%). The chest generally sounds clear without crackles or wheeze, and the chest radiograph shows prominent perihilar pulmonary vascular markings, fluid in the intralobar fissures, and rarely small pleural effusions (Fig. 128.1). Hypercapnia and acidosis are uncommon. Respiratory failure requiring positive pressure support (either with nasal continuous positive airway pressure [nCPAP] or mechanical ventilation) also is uncommon, but when it occurs usually resolves rapidly (<12-24 hours). Most infants recover with supportive care alone, and over the first 24-72 hours the tachypnea and O_2 requirements slowly resolve.

DIAGNOSIS

Distinguishing TTN from respiratory distress syndrome (RDS) and other respiratory disorders (e.g., pneumonia) may be difficult, and transient tachypnea is frequently a diagnosis of exclusion. The distinctive features of TTN are rapid recovery of the infant and the absence of radiographic findings for RDS (low lung volumes, diffuse reticulogranular pattern, air bronchograms) and other lung disorders. Other respiratory disorders to consider include meconium aspiration syndrome (see Chapter 129), persistent pulmonary hypertension of the newborn (see Chapter 130), congenital lung anomalies, and spontaneous air leak (see Chapter 132). **Primary ciliary dyskinesia (PCD)** often presents in the newborn period and may resemble TTN or RDS. PCD in the newborn often lasts longer than TTN and requires a longer duration of oxygen therapy (Chapter 455).

PREVENTION

Prevention of TTN generally focuses on avoidance of modifiable risk factors. As prematurity increases the risk of TTN, the American College of Obstetrics and Gynecology recommends against nonmedically indicated deliveries, either vaginal or cesarean, before 39 weeks. They further state that documentation of fetal lung maturity, previously accomplished via amniocentesis with amniotic fluid testing, should not be used to guide early delivery as this does not ensure appropriate maturation of physiologic processes. When late-preterm delivery is medically indicated or threatened, the use of a single course of antenatal steroids is associated with a decreased risk of TTN and may be considered. Use of antenatal steroids at increasing gestational ages must be balanced against an increased risk of hypoglycemia in the neonate postpartum.

TREATMENT

Treatment for TTN is supportive. Based on the degree of symptoms and progression of those symptoms over the first 2 hours after birth, transfer to a facility with appropriate neonatal intensive care unit (NICU) care may be required. Supplemental oxygen should be provided to maintain saturations over 90%. nCPAP can be used to support infants with more significant work of breathing or oxygen requirements. Further evaluation with chest radiograph or blood gas analysis can be undertaken when distress is more significant, or the diagnosis is in question. Infants with significant tachypnea may be unable or unsafe to feed orally and can be supported with intravenous fluids or nasogastric feedings. Generally, TTN is unrelated to an underlying infection; however, antibiotic coverage may be initiated in patients with additional risk factors. Further evaluation for an alternate diagnosis should be undertaken if symptoms are not resolving by 72 hours of age.

Inhaled β_2-agonists such as albuterol (salbutamol) increase expression and activation of ENaC and Na^+,K^+-ATPase and facilitate fluid clearance. Emerging evidence suggests that when given early in the course of TTN, albuterol may improve oxygenation, shorten the duration of supplemental O_2 therapy, and expedite recovery; however, more data are needed before employing this method.

PROGNOSIS

Infants with a history of TTN do have an increased risk of developing a wheezing diagnosis during childhood. This association persists even after stratifying for the underlying risk factor of maternal asthma.

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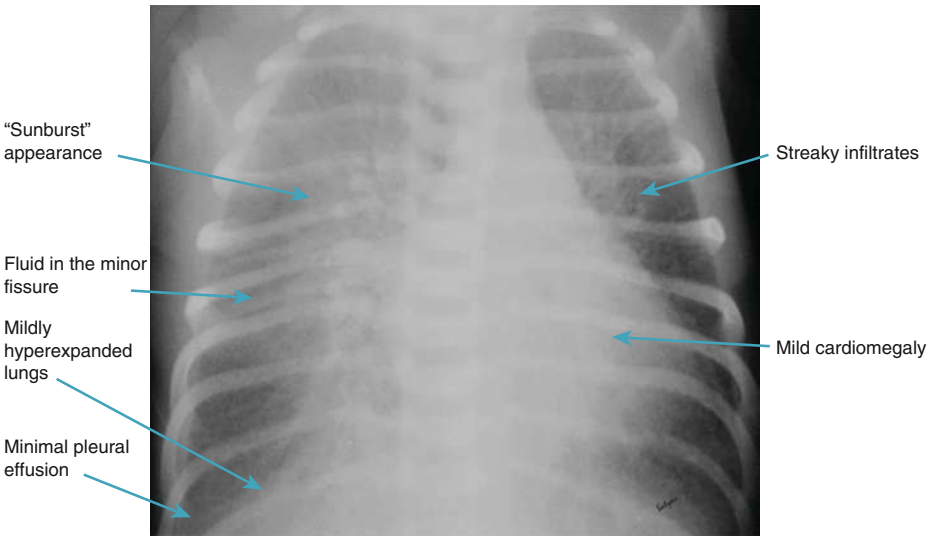

Fig. 128.1 Chest radiograph of an infant with transient tachypnea of the newborn. Notable features include increased pulmonary markings particularly in the perihilar region and fluid in the fissure. This contrasts with the radiograph of an infant with respiratory distress syndrome, which generally includes a homogenous ground glass appearance and hypoinflation. *(From Alhassen Z, Vali P, Guglani L, Lakshminrusimha S, Ryan RM. Recent advances in pathophysiology and management of transient tachypnea of newborn. J Perinatol. 2021;41:6–16. Fig. 5.)*

Chapter 129

Aspiration of Foreign Material (Meconium Aspiration Syndrome, Aspiration Pneumonia)

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Aspiration in the neonate can occur intrapartum often as a result of fetal distress or aspiration may occur postpartum, which can be related to a number of conditions including cardiopulmonary dysfunction, gastroesophageal reflux, aerodigestive tract anomalies, neurodevelopmental impairment, and craniofacial abnormalities.

INTRAPARTUM ASPIRATION

With fetal distress, the fetus often initiates vigorous respiratory movements in utero because of interference with the supply of oxygen through the placenta. Under such circumstances, the infant may aspirate amniotic fluid containing vernix caseosa, epithelial cells, meconium, blood, or material from the birth canal, which may block the smallest airways and interfere with alveolar exchange of O_2 and CO_2. Pathogenic bacteria may accompany the aspirated material, and pneumonia may ensue, but even in noninfected cases, respiratory distress accompanied by radiographic evidence of aspiration is seen (Fig. 129.1). The most relevant consequences of intrapartum aspiration are pneumonia and meconium aspiration syndrome (MAS).

Early-Onset Sepsis and Neonatal Pneumonia

Pneumonia as a presentation of early-onset sepsis typically arises following aspiration of infected amniotic fluid (see Chapter 149). The incidence of early-onset sepsis is 0.5 per 1,000 among term infants and increases to 1 per 1,000 among late preterm infants. The mortality rate is 2–3%. The most common causative agent is group B streptococcus (GBS; 40–45% of cases). Other causative agents include *Escherichia coli* and other gram-negative rods (10–15% of cases), *Enterococcus faecalis*, *Staphylococcus aureus*, and *Listeria monocytogenes*.

Bacteria within the airways causes direct mucosa injury, surfactant dysfunction, pulmonary edema, mechanical airway obstruction due to inflammation and debris, and can trigger vasoconstriction and pulmonary hypertension. Infants are particularly susceptible to infection due to immaturity of their innate and adaptive immune systems, a risk factor that is more pronounced in premature or growth-restricted infants. Additional risk factors for infection include being male, known maternal colonization with GBS, maternal fever, and prolonged rupture of membranes (>18 hours).

Diagnosis of neonatal pneumonia includes radiographic evidence of infiltrate, and consolidation, and less often cavitation or pneumatocele. Infants will display hypoxic and hypercarbic respiratory failure with frequent need for invasive ventilation; hypotension is common. Temperature instability, particularly hypothermia, is also common. White blood cell counts and single values of inflammatory markers have limited predictive potential. Blood cultures are indicated, and cerebrospinal fluid should be obtained if the blood culture is positive.

Treatment of neonatal pneumonia includes the prompt initiation of empiric broad-spectrum antibiotics. Commonly, ampicillin and an aminoglycoside (gentamicin) are used as first-line therapy with the substitution of a cephalosporin or meropenem in place of the aminoglycoside when meningitis is a concern or in cases of suspected antibiotic resistance. Therapy is typically 7-14 days in duration and should be completed parenterally.

Prevention of early-onset sepsis has largely involved the targeted intrapartum antibiotic prophylaxis of mothers known to be colonized with GBS. GBS prophylaxis, generally penicillin, is indicated for women who screen positive for colonization via vaginal-rectal culture at 36-37 weeks' gestation, have a history of an infant affected by GBS disease, or for preterm labor when GBS status is unknown. Additional broad-spectrum antibiotic therapy is indicated for women with intrapartum fever to decrease risk of ascending infection.

For more information on early-onset sepsis see Chapter 149.

Meconium Aspiration Syndrome

Meconium-stained amniotic fluid is found in 10–15% of births and usually occurs in term or postterm infants. MAS develops in 5% of such infants; 30% require mechanical ventilation, and 3–5% die. Usually, but

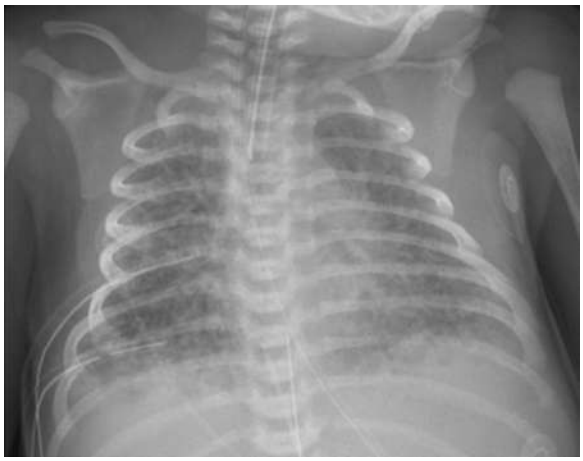

Fig. 129.1 Anteroposterior chest radiograph of a term infant with meconium aspiration syndrome shows the typical pattern of mixed atelectasis and local emphysema. An endotracheal tube is seen in good position. Two chest tubes are present in the right chest without persistent pneumothorax. *(From Rodriguez NE. Assessment of the neonatal and pediatric patient. In Heuer AJ, ed. Wilkins' Clinical Assessment in Respiratory Care, 9th ed. Philadelphia: Elsevier; 2022: Fig. 12.17)*

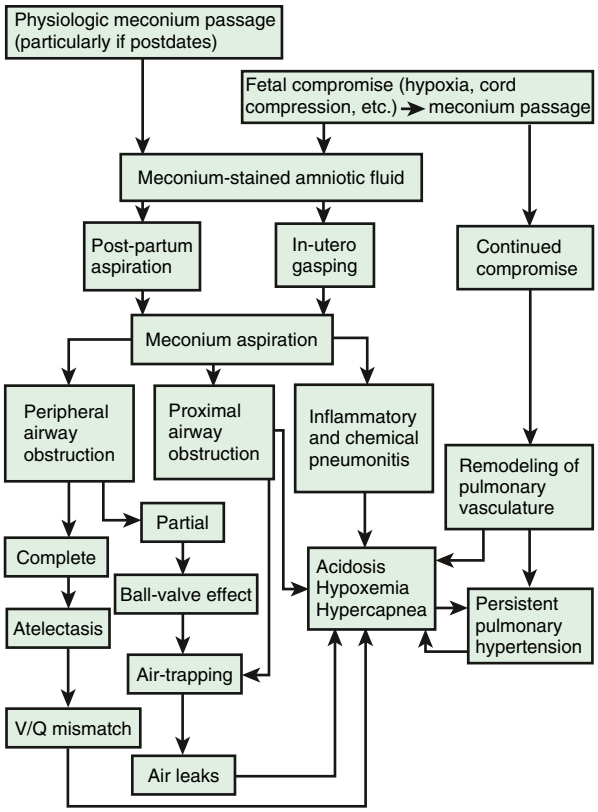

Fig. 129.2 Pathophysiology of meconium passage and the meconium aspiration syndrome. V/Q, ventilation-perfusion ratio. *(From Wiswell TE, Bent RC. Meconium staining and the meconium aspiration syndrome: unresolved issues. Pediatr Clin North Am. 1993;40:955–981.)*

not invariably, fetal distress and hypoxia occur before the passage of meconium into amniotic fluid. The infants are meconium stained and may be depressed and require resuscitation at birth. Either in utero or with the first breath, thick, particulate meconium is aspirated into the lungs. Partial obstruction of some airways may lead to pneumomediastinum, pneumothorax, or both. Overdistention of the chest may be prominent. Meconium within the lungs causes a chemical pneumonitis leading to surfactant dysfunction and inflammation (Fig. 129.1). The combination of airway obstruction and chemical injury can contribute to the development of persistent pulmonary hypertension of the newborn (PPHN; see Chapter 130). The pathophysiology of MAS is further described in Figure 129.2.

The clinical presentation of MAS is that of respiratory distress and cyanosis. In cases where in utero hypoxia was present, the presentation of MAS may be compounded by hypoxic ischemic encephalopathy and multiorgan dysfunction (including myocardial injury). The condition usually improves within 72 hours, but when its course requires assisted ventilation, it may be severe, prolonged, and with a risk for mortality. Tachypnea may persist for many days or even several weeks. The typical chest radiograph is characterized by patchy infiltrates, coarse streaking of both lung fields, increased anteroposterior diameter, and flattening of the diaphragm with possible pneumothorax (see Fig. 129.1).

The risk of meconium aspiration may be decreased by rapid identification of fetal distress and initiation of prompt delivery. Intrapartum nasopharyngeal suctioning in infants with meconium-stained amniotic fluid does not reduce the risk for MAS. Routine intubation and aspiration of depressed infants (those with hypotonia, bradycardia, or decreased respiratory effort) born through meconium-stained fluid is not effective in reducing the MAS or other major adverse outcomes and is not recommended for neonatal resuscitation. The risk of meconium-stained amniotic fluids increases with increasing gestational age. Additionally, among those infants with meconium-stained fluids, the risk for MAS increases with increasing gestational age (4.8% at >42 weeks vs 2.6% at 40 weeks) therefore limiting significantly postterm deliveries (>42 weeks) decreases the incidence of MAS.

Treatment of MAS includes supportive care and standard management for respiratory distress. The beneficial effect of mean airway pressure on oxygenation must be weighed against the risk of pneumothorax. Administration of exogenous surfactant and/or inhaled nitric oxide (iNO) to infants with MAS and hypoxemic respiratory failure, or pulmonary hypertension requiring mechanical ventilation, decreases the need for extracorporeal membrane oxygenation (ECMO), which is required by the most severely affected infants who show no response to therapy. In infants with MAS who demonstrate no other signs of sepsis, there is no role for continued antibiotic therapy. Severe meconium aspiration may be complicated by persistent pulmonary hypertension. Patients with MAS refractory to conventional mechanical ventilation may benefit from high-frequency ventilation (HFV) or ECMO (see Chapter 130). Management may also include concurrent treatment for hypoxic injury as discussed in Chapter 120.

The mortality rate of meconium-stained infants is considerably higher than that of nonstained infants. The decline in neonatal deaths caused by MAS is related to improvements in obstetric and neonatal care. Residual lung problems are rare but include symptomatic cough, wheezing, and persistent hyperinflation for up to 5-10 years. The ultimate prognosis depends on the extent of central nervous system injury from asphyxia and the presence of associated problems such as pulmonary hypertension.

POSTPARTUM ASPIRATION

Aspiration in the newborn after birth can be globally divided into categories of anatomic abnormalities and swallowing dysfunction. Regardless of the cause, the consequences of aspiration include pneumonia, chemical pneumonitis, and airway swelling.

Anatomic Causes of Postpartum Aspiration

Abnormalities of the aerodigestive tract can contribute to the passage of oral secretions and milk into the lungs. Obstruction or narrowing of the nasal cavity or nasopharynx can interrupt the normal

suck-swallow-breath cycle of the infant and increase the risk of aspiration. These conditions include genetic disorders associated with midface hypoplasia, choanal atresia, and congenital nasal masses or tumors. Infants with nasal obstruction will present with stertor, cyanosis improved with crying, and an inability to pass a nasal feeding tube. Oral sources of aspiration include micrognathia/retrognathia and oral masses that compromise airway protection. Cleft lip and palate can impair velopharyngeal closure and increase nasal regurgitation of milk with subsequent aspiration. Anatomic causes of aspiration at the level of the larynx include laryngomalacia due to increased work of breathing with poorer airway protective mechanisms, laryngotracheoesophageal clefts, and vocal fold paralysis or paresis where aspiration occurs as the vocal folds are unable to adduct and protect the airway. Tracheoesophageal fistula (TEF) contributes to aspiration via a direct connection between the esophagus and the airway. TEF can be divided into five types based on the location of the fistula and presence of esophageal atresia. Prenatal diagnosis may occur after the recognition of polyhydramnios and a small fetal stomach. Postnatal symptoms include excessive salivation that worsen with feeding attempts, choking, cough, cyanosis, respiratory distress, and an inability to pass an orogastric (OG) tube. TEF should prompt an evaluation for other anomalies.

When an anatomic abnormality is believed to be contributing to aspiration, initial management should include cessation of feeding pending an evaluation. Some conditions including vocal fold paresis and laryngomalacia may resolve spontaneously, and modified feeding strategies, often under the direction of a speech language pathologist, can allow delivery of nutrition until the condition improves with time and growth. Cleft palate can often be managed with feeding modification until surgical repair in infancy. Other conditions including choanal atresia and TEF require surgical intervention in the newborn period. In some cases, tracheostomy is required for infants unable to adequately protect their airway. Although reflux alone is not the cause of aspiration in these cases, decreasing the acidity of the aspirate may decrease airway swelling, and antireflux medications can be considered in select populations.

Swallowing Dysfunction

Swallowing dysfunction is another cause of aspiration in the newborn. Swallowing is a complex process and must be coordinated with respirations. Infants with neurologic injury may display abnormalities in the swallowing reflex or in the recognition and prevention of aspiration. Infants with pulmonary or cardiovascular disease leading to tachypnea will have more trouble coordinating a suck-swallow-breath cycle. Premature infants are more likely to have swallowing dysfunction because of prematurity-related pulmonary insufficiency and because of immaturity of the swallow mechanism, which begins to mature between 32 and 34 weeks. Hypotonic infants due to neuromuscular diseases or as a sequalae of hypoxic-ischemic encephalopathy are at increased risk of aspiration.

Evaluation of the swallow in at-risk infants often occurs with the assistance of a speech language pathologist and may include video fluoroscopic swallow studies to evaluate swallowing pattern and document aspiration. A fiberoptic endoscopic evaluation of the swallow (FEES) is another strategy whereby a speech language pathologist and ear, nose, and throat doctor observe a small-volume swallow via direct endoscopic visualization. Neurologic imaging may be indicated to assess for the underlying etiology of an ineffective or uncoordinated swallow.

Treatment strategies include feeding modifications such as pacing (tilting the bottle down every three to five sucks to allow recovery time), modified feeding position, or using a slower flow nipple. In cases where feeding modification does not adequately improve swallow safety, a percutaneous gastric tube for feeding may be indicated.

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Chapter 130

Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Persistent pulmonary hypertension of the newborn (PPHN) predominantly occurs in term and postterm infants. Predisposing factors include birth asphyxia, meconium aspiration syndrome (MAS), early-onset sepsis, respiratory distress syndrome (RDS), hypoglycemia, polycythemia, maternal use of nonsteroidal antiinflammatory drugs with in utero constriction of the ductus arteriosus, maternal late trimester use of selective serotonin reuptake inhibitors, and pulmonary hypoplasia caused by diaphragmatic hernia (Table 130.1). PPHN is often idiopathic. Some patients with PPHN have low plasma arginine and nitric oxide (NO) metabolite concentrations and polymorphisms of the carbamoyl phosphate synthase gene, findings suggestive of a possible subtle defect in NO production. The incidence is 1 in 500-1,500 live births, with a wide variation among clinical centers. Regardless of etiology of PPHN, profound hypoxemia from right-to-left shunting and normal or elevated $Paco_2$ are present (Fig. 130.1).

PATHOPHYSIOLOGY

Persistence of the fetal circulatory pattern of right-to-left shunting through the patent ductus arteriosus (PDA) and foramen ovale after birth is a result of excessively high pulmonary vascular resistance (PVR). Fetal PVR is usually elevated relative to fetal systemic or postnatal pulmonary pressure. This fetal state normally permits shunting of oxygenated umbilical venous blood to the left atrium (and brain) through the foramen ovale, from which it bypasses the lungs through the ductus arteriosus and passes to the descending aorta. After birth, PVR normally declines rapidly as a consequence of vasodilation secondary to lung inflation, a rise in postnatal Pao_2, a reduction in $Paco_2$, increased pH, and release of vasoactive substances. Increased neonatal PVR may be (1) **maladaptive** from an acute injury (not demonstrating normal vasodilation in response to increased O_2 and other changes after birth); (2) the result of increased pulmonary artery medial muscle thickness and extension of smooth muscle layers into the usually nonmuscular, more peripheral pulmonary arterioles in response to chronic fetal hypoxia; (3) a consequence of **pulmonary hypoplasia** (diaphragmatic hernia, Potter syndrome); or (4) **obstructive** as a result of polycythemia, total anomalous pulmonary venous return (TAPVR), or congenital diffuse development disorders of acinar lung development.

CLINICAL MANIFESTATIONS

PPHN usually manifests in the delivery room or within the first 12 hours after birth. Idiopathic PPHN or PPHN related to polycythemia, hypoglycemia, hypothermia, or asphyxia may result in severe cyanosis and respiratory distress. In some cases, however, initial signs of respiratory distress may be minimal. Infants who have PPHN associated with meconium aspiration, group B streptococcal pneumonia, diaphragmatic hernia, or pulmonary hypoplasia usually exhibit cyanosis, grunting, flaring, retractions, tachycardia, and shock. Multiorgan involvement may be present. Myocardial ischemia, papillary muscle dysfunction with mitral and tricuspid regurgitation, and biventricular dysfunction produce cardiogenic shock with decreases in pulmonary blood flow, tissue perfusion, and O_2 delivery.

Table 130.1 Etiology of Persistent Pulmonary Hypertension of the Newborn in Neonates

Maladaptation of pulmonary vasculature (abnormal, "reactive" pulmonary vasoconstriction)
- Parenchymal lung diseases, such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), and pneumonia
- In response to systemic disorders, such as hypothermia, sepsis, fetal hypoxia/distress, hypercapnia, acidosis, and hyperviscosity
- Toxic/pharmacologic exposure in utero (maternal selective serotonin reuptake inhibitor (SSRI) use)

Maldevelopment of pulmonary vasculature (remodeling of pulmonary vasculature)
- In utero closure of ductus arteriosus (maternal cyclooxygenase inhibitor use)
- Sustained pulmonary over circulation in congenital heart disease with large left-to-right shunts
- Intrauterine growth restriction
- Genetic/chromosomal anomalies (trisomy 21, alveolar-capillary dysplasia, surfactant protein deficiency)

Underdevelopment of pulmonary vasculature (hypoplastic pulmonary vessels; ↓ cross-sectional area)
- Congenital diaphragmatic hernia
- Pulmonary hypoplasia (premature prolonged rupture of membranes, oligohydramnios and anhydramnios, space-occupying lesions in the chest).

From Sharma M, Callan E, Konduri GG. Pulmonary vasodilator therapy in persistent pulmonary hypertension of the newborn. *Clin Perinatol*. 2022;49:103–105. Box 1.

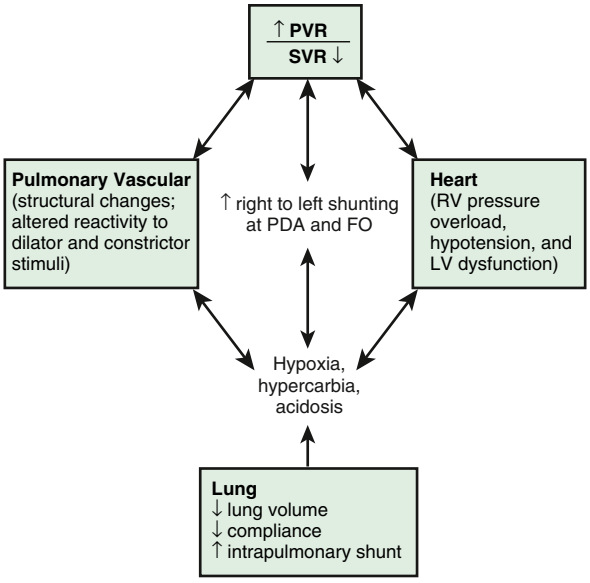

Fig. 130.1 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn (PPHN). FO, Foramen ovale; LV, left ventricle; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricle; SVR, systemic vascular resistance. *(From Kinsella JP, Abman SH. Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. J Pediatr. 1995;126:853–864.)*

Hypoxemia is often labile and out of proportion to the findings on chest radiographs. In PPHN due to asphyxia and idiopathic PPHN, chest x-ray findings are often normal, whereas in PPHN associated with pneumonia and diaphragmatic hernia, parenchymal opacification and bowel/liver in the chest, respectively, are seen.

DIAGNOSIS

Independent of the prenatal history, PPHN should be suspected in all term infants who have cyanosis. Hypoxemia is universal and intermittently unresponsive to 100% O_2 given by oxygen hood or nasal

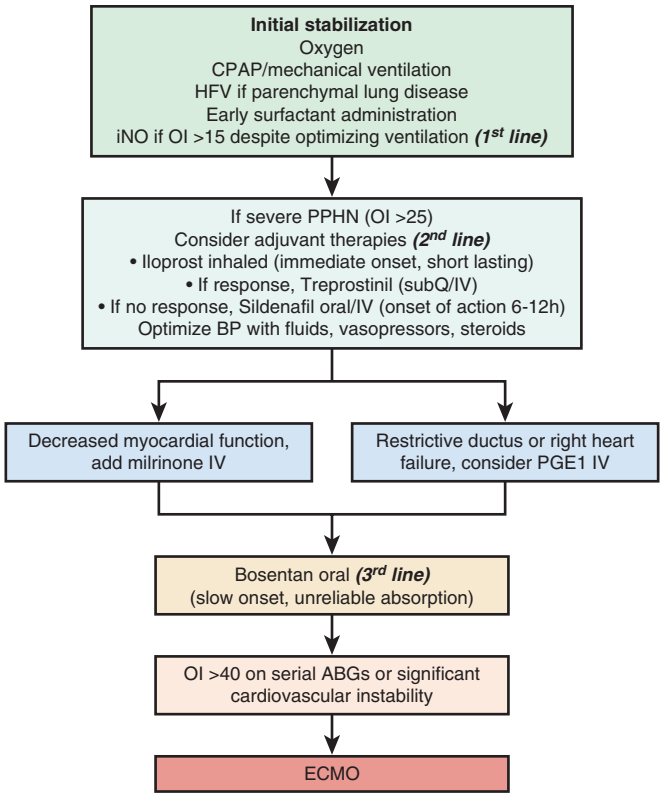

Fig. 130.2 Algorithm for the suggested approach and timing of interventions for the management of hypoxic respiratory failure (HRF)/persistent pulmonary hypertension of the newborn (PPHN). It is important to consider cardiopulmonary system to be one fully integrated unit and optimize lung recruitment, pulmonary vasodilation, and cardiac function to facilitate successful transition. The algorithm focuses on vasodilator agents and is not meant to be inclusive of all therapies used in the management of PPHN. ABG, Arterial blood gas; BP, blood pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; HFV, high-frequency ventilation; iNO, inhaled nitric oxide; IV, intravenous; OI, oxygenation index; PGE1, prostaglandin E1; subQ, subcutaneous. *(From Sharma M, Callan E, Konduri GG. Pulmonary vasodilator therapy in persistent pulmonary hypertension of the newborn. Clin Perinatol. 2022;49:103–105, Fig. 3.)*

cannula. A Pao_2 or Sao_2 gradient between a preductal (right radial artery) and a postductal (umbilical artery) site of blood sampling suggests right-to-left shunting through the ductus arteriosus. Intracardiac shunting through the patent foramen ovale does not lead to a Pao_2 or Sao_2 gradient.

Real-time echocardiography combined with Doppler flow imaging is very helpful in evaluating PPHN. Systolic flattening of the interventricular septum as the right ventricular systolic pressure approaches the left ventricular systolic pressure can be used to estimate the degree of pulmonary hypertension. The peak velocity of the tricuspid valve regurgitation jet, when present, yields a quantitative estimate of the right ventricular systolic pressure. Likewise, the direction and velocity of a shunt across the PDA provides a quantitative comparison between the aortic and pulmonary artery pressures. In advanced cases, right-to-left or bidirectional shunting across a PDA and a patent foramen ovale can be observed.

The differential diagnosis of PPHN includes cyanotic heart disease (especially obstructed TAPVR), idiopathic pulmonary vein stenosis, congenital surfactant (protein) deficiency syndromes, pulmonary artery thrombosis, and congenital diffuse development disorders of acinar lung development (acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins).

Alveolocapillary dysplasia (ACD) is a rare, lethal autosomal recessive disorder of distal lung development characterized by immature lobular development and reduced capillary density. Infants with ACD

present with idiopathic PPHN, demonstrating little or no parenchymal lung disease and profound hypoxemia. Over 60% of infants with ACD manifest hypoxemia and respiratory failure within 48 hours of birth, while some with milder disease present beyond 6 months of age. The diagnosis is made on autopsy in 90% of cases, and the constellation of findings include thickened alveolar septa, increased muscularization of the pulmonary arterioles, a reduced number of capillaries, with the remaining capillaries demonstrating abnormal apposition to the air interface, and misalignment of the intrapulmonary veins. In up to 80% of cases, extrapulmonary malformations of the genitourinary, gastrointestinal, or cardiovascular system are present. Pathogenic variants in the transcription factor gene *FOXFI* have been identified in up to 40% of cases, but the diagnosis continues to rest on clinical and histopathologic features. There also may be associated gastrointestinal (malrotation), genitourinary, and cardiac (hypoplastic left heart syndrome) malformations. ACD is uniformly lethal and should be suspected in infants with idiopathic PPHN who fail to respond to maximal medical therapy, or when symptoms recur after successful weaning from extracorporeal membrane oxygenation (ECMO). In a UK ECMO report, up to 14% of infants who failed ECMO ultimately were diagnosed with ACD. Regardless of the timing of presentation, ACD is uniformly fatal, and lung transplantation remains the sole, experimental therapy.

TREATMENT

Therapy for PPHN is directed toward correcting any predisposing condition (e.g., hypoglycemia, polycythemia) and improving poor tissue oxygenation by addressing the underlying pathology (Fig. 130.2). Initial management includes O_2 administration and correction of acidosis, hypotension, and hypercapnia. Persistent hypoxemia should be managed with intubation and mechanical ventilation.

Infants with PPHN are usually managed *without* hyperventilation or alkalization. Gentle ventilation with normocarbia or permissive hypercarbia and avoidance of hypoxemia result in excellent outcomes and a low incidence of chronic lung disease and ECMO use.

Because of their instability and ability to fight the ventilator, newborns with PPHN usually require sedation. Nonpharmacologic measures such as minimal noise, light, and tactile stimulation are also employed. The use of paralytic agents is controversial and reserved for the newborn who cannot be treated with sedatives alone. Muscle relaxants may promote atelectasis of dependent lung regions and ventilation-perfusion mismatch and may be associated with an increased risk of death.

Inotropic therapy is frequently needed to support blood pressure and perfusion. Whereas epinephrine is frequently used as a first-line agent, other agents, such as dobutamine and milrinone, may be helpful when myocardial contractility is poor. Many centers use echo-guided assessment of cardiac function to choose appropriate inotropic therapy. Dopamine is typically avoided due to its ability to increase PVR. Some of the sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamines by overwhelming illness and relative adrenal insufficiency. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency.

Inhaled nitric oxide (iNO) is an endothelium-derived signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by inhalation. *Use of iNO reduces the need for ECMO support by approximately 40%.* The optimal starting dose is 20 ppm. Higher doses have not been shown to be more effective and are associated with side effects, including methemoglobinemia and increased levels of nitrogen dioxide, a pulmonary irritant. Most newborns require iNO for <5 days. Although iNO has been used as long-term therapy in children and adults with primary pulmonary hypertension, prolonged dependency is rare in neonates and suggests the presence of lung hypoplasia, congenital heart disease, or ACD. The maximal safe duration of iNO therapy is unknown. The infant can be weaned to 5 ppm after 6-24 hours of therapy. The dose can then be reduced slowly and discontinued when F_{IO_2} is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided because it may cause rebound pulmonary hypertension. iNO should be used only at institutions that offer ECMO support or have the capability of transporting an infant on iNO therapy if a referral for ECMO is necessary. Some infants with PPHN do not respond adequately to iNO. Therapy with continuous inhaled or intravenous (IV) prostacyclin (prostaglandin I_2) can improve oxygenation in infants with PPHN. The safety and efficacy of sildenafil (type 5 phosphodiesterase inhibitor) in newborns with PPHN is under investigation; initial results are promising.

In 5–10% of patients with PPHN, the response to 100% O_2, mechanical ventilation, and drugs is poor, and many of these infants benefit from ECMO. In such patients, two parameters have been used to predict mortality: the alveolar-arterial oxygen gradient ($P_A\text{-}aO_2$), and the oxygenation index (OI), calculated as F_{IO_2} (as %) × MAP/P_{aO_2}. A $P_A\text{-}aO_2$ >600 for 8-12 hours and an OI >40 unresponsive to iNO predict a high mortality rate (>80%) and are indications for ECMO. In carefully selected, severely ill infants with hypoxemic respiratory failure caused by RDS, meconium aspiration pneumonia, congenital diaphragmatic hernia, PPHN, or sepsis, ECMO significantly improves survival.

ECMO is a form of cardiopulmonary bypass that augments systemic perfusion and provides gas exchange. Most experience has been with *venoarterial bypass,* which requires carotid artery ligation and the placement of large catheters in the right internal jugular vein and carotid artery. *Venovenous bypass* avoids carotid artery ligation and provides gas exchange, but it does not support cardiac output. Blood is initially pumped through the ECMO circuit at a rate that approximates 80% of the estimated cardiac output (150-200 mL/kg/min). Venous return passes through a membrane oxygenator, is rewarmed, and returns to the aortic arch in venoarterial ECMO and to the right atrium in venovenous ECMO. Venous O_2 saturation values are used to monitor tissue O_2 delivery and subsequent extraction for infants undergoing venoarterial ECMO, whereas arterial O_2 saturation values are used to monitor oxygenation for infants receiving venovenous ECMO.

Because ECMO requires complete heparinization to prevent clotting in the circuit, its use is generally avoided in patients with existing intracranial hemorrhage or who are at high risk of developing intraventricular hemorrhage (weight <2 kg, gestational age <34 weeks). In addition, infants being considered for ECMO should have reversible lung disease, no signs of systemic bleeding, and no severe asphyxia or lethal malformations, and they should have been ventilated for <10 days. Complications of ECMO include thromboembolism, air embolization, bleeding, stroke, seizures, atelectasis, cholestatic jaundice, thrombocytopenia, neutropenia, hemolysis, infectious complications of blood transfusions, edema formation, and systemic hypertension.

PROGNOSIS

Survival in patients with PPHN varies with the underlying diagnosis but is generally ~90%. Long-term, survivors of PPHN are at risk for neurodevelopmental impairment and sensorineural deafness, which can occur in about 25% of patients. The outcome for infants with PPHN who are treated with ECMO is also favorable; >80–90% survive, and 60–75% of survivors appear normal at 1-3.5 years of age.

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Chapter 131

Diaphragmatic Hernia

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax (Fig. 131.1). The etiology is rarely traumatic and usually congenital. The symptoms and prognosis depend on the location of the defect and associated anomalies. The defect may be at the esophageal hiatus **(hiatal hernia)**; paraesophageal, adjacent to the hiatus (**paraesophageal hernia**; see Chapter 131.2); retrosternal (**foramen of Morgagni hernia**; see Chapter 131.1); or at the posterolateral portion of the diaphragm **(Bochdalek hernia)**. In **congenital diaphragmatic hernia (CDH),** the Bochdalek hernia accounts for up to 90% of the hernias seen, with 80–90% occurring on the left side. The Morgagni hernia accounts for 2–6% of CDH. The size of the defect is highly variable, ranging from a small hole to complete agenesis of this area of the diaphragm. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity.

CONGENITAL DIAPHRAGMATIC HERNIA (BOCHDALEK)

Pathology and Etiology

Although CDH is characterized by a structural diaphragmatic defect, a major limiting factor for survival is the association with other anomalies, syndromes, and primarily with pulmonary hypoplasia. Lung hypoplasia was initially thought to be solely caused by the compression of the lung from the herniated abdominal contents, which impaired lung growth. However, evidence indicates that pulmonary hypoplasia, at least in some cases, may precede the development of the diaphragmatic defect.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles, and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal saccules, thickened alveoli, and thickened pulmonary arterioles. Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli, and decreased levels of phosphatidylcholine, total DNA, and total lung protein, all of which contribute to limited gas exchange.

Epidemiology

The incidence of CDH is between 1 in 2,000 and 1 in 3,000 live births, with males affected more often than females. Defects are more common on the left (85%) and are occasionally bilateral (<5%). Pulmonary hypoplasia and malrotation of the intestine are part of the lesion, not associated anomalies. Most cases of CDH are nonsyndromic (sporadic; 60%), but familial and syndromic cases have been reported. Associated anomalies in nonsyndromic patients have been reported in up to 30% of cases, including hypoplastic left heart syndrome and accessory spleens. CDH is recognized as part of several aneuploidy syndromes: trisomies 21, 13, and 18 and those with copy number variation: del 15q26.1-q26.2, del 8p23.1, del 1q41-q42, and del 4p16.3 as well as definable single gene syndromes including Cornelia de Lange, Donnai-Barrow, Cutis Laxa, cardiac-urogenital, and Matthew-Wood syndromes.

Diagnosis and Clinical Presentation

In >50% of cases, CDH can be diagnosed on prenatal ultrasonography (US) between 16 and 24 weeks of gestation. High-speed fetal MRI can further define the lesion. US findings may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity, and fetal hydrops. Certain imaging features may predict outcome including liver position in the chest, observed-to-expected total lung volume (O/E TLV), and observed-to-expected lung-to-head ratio (O/E LHR). Nonetheless, no definitive characteristic reliably predicts outcome. After delivery, a chest radiograph is needed to confirm the diagnosis (Fig. 131.2). In some infants with an echogenic chest mass, further imaging is required. The differential diagnosis may include other diaphragm disorders, such as eventration or a cystic lung lesion (pulmonary sequestration, cystic adenomatoid malformation).

Arriving at the diagnosis early in pregnancy allows for prenatal counseling, possible fetal interventions (see Chapter 118), and planning for postnatal care. A referral to a center providing high-risk obstetrics, pediatric surgery, and tertiary care neonatology is advised. Careful evaluation for other anomalies should include echocardiography and amniocentesis. To avoid unnecessary pregnancy termination and unrealistic expectations, an experienced multidisciplinary group must carefully counsel the parents of a child diagnosed with a diaphragmatic hernia.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth, or there may be a period of up to 48 hours during which the baby is relatively stable. Respiratory distress

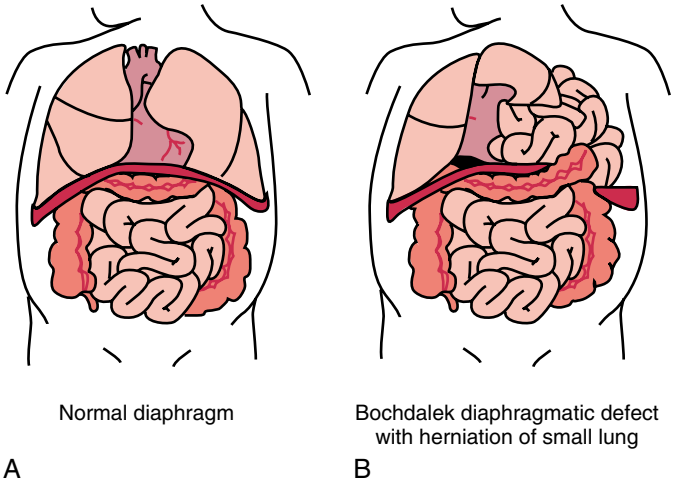

Fig. 131.1 A, Normal diaphragm separating the abdominal and thoracic cavity. B, Diaphragmatic hernia with a small lung and abdominal contents in the thoracic cavity.

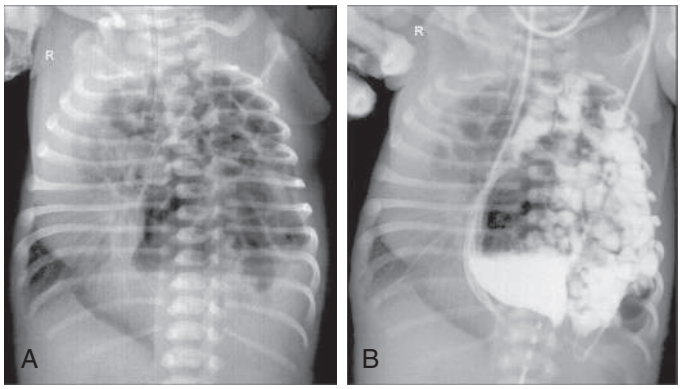

Fig. 131.2 Bochdalek hernia. A, Chest radiograph showing herniated bowel loops in the left hemithorax, displacement of the mediastinum to the contralateral side, severely reduced lung space, and unclear lung fields bilaterally. B, Upper gastrointestinal tract radiograph showing the stomach and bowel loops stained with contrast in the left hemithorax. *(From Hu X, Liu B. Bochdalek hernia. Lancet. 2018;392:60.)*

is characterized clinically by tachypnea, grunting, use of accessory muscles, and cyanosis. Children with CDH may also have a scaphoid abdomen and increased chest wall diameter. Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest radiograph and passage of a gastric tube are usually sufficient to confirm the diagnosis.

A small group of infants with CDH present beyond the neonatal period. Patients with a delayed presentation may experience vomiting as a result of intestinal obstruction or mild respiratory symptoms. Occasionally, incarceration of the intestine proceeds to ischemia with sepsis and shock. Unrecognized diaphragmatic hernia is a rare cause of sudden death in infants and toddlers. Group B streptococcal sepsis has been associated with delayed onset of symptoms and a CDH (often right side).

Treatment

Initial Management

Delivery at a tertiary center with experience in the management of CDH is required to provide early, appropriate respiratory support. In the delivery room, infants with respiratory distress should be rapidly stabilized with endotracheal intubation. *Prolonged mask ventilation in the delivery room, which enlarges the stomach and small bowel and thus makes oxygenation more difficult, must be avoided and a nasogastric or orogastric tube placed immediately for decompression.* Once in the neonatal intensive care unit (NICU), central arterial and venous (umbilical) lines are placed, pre- and postductal saturations monitored, and gastric contents intermittently decompressed to prevent enlargement. A preductal arterial oxygen saturation (Spo_2) value ≥85% should be the minimum goal. An initial arterial Pco_2 >80 mm Hg is predictive of mortality in infants with CDH. Volutrauma is a significant problem. *Gentle ventilation with permissive hypercapnia* reduces lung injury, need for extracorporeal membrane oxygen (ECMO), and mortality. Factors that contribute to persistent pulmonary hypertension of the newborn (PPHN; hypoxia, acidosis, hypothermia) should be avoided (see Chapter 130). Echocardiography is important to guide therapeutic decisions by measuring pulmonary and system vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Neonates with CDH may be surfactant deficient. Although surfactant is frequently used, no study has proved that it is beneficial in treatment of CDH, and it may precipitate decompensation. In infants with severe respiratory failure and hypoxemia, sedation and paralysis may be required.

Ventilation Strategies

Conventional mechanical ventilation, high-frequency oscillatory ventilation (HFOV), and ECMO are the three main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and CO_2 elimination without inducing volutrauma. Conventional ventilation using a gentle, lung protective strategy (peak inspiratory pressure [PIP] <25, positive end-expiratory pressure [PEEP] 3-5 cm H_2O) that allows for permissive hypercapnia ($Paco_2$ <65 mm Hg) is recommended. Permissive hypercapnia (as opposed to hyperventilation with high PIP) has reduced lung injury and improved survival. HFOV as a rescue therapy is indicated if a PIP >25 is required to maintain appropriate ventilation or if hypoxemia persists.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator. Its use reduces ductal shunting and pulmonary pressures and results in improved oxygenation. Although iNO has been helpful in PPHN, randomized trials have not demonstrated improved survival or reduced need for ECMO when iNO is used in newborns with CDH. Nonetheless, iNO is used in patients with CDH as a bridge to ECMO.

Extracorporeal Membrane Oxygenation

The availability of ECMO and the utility of preoperative stabilization has improved survival of babies with CDH. ECMO is the therapeutic option for children in whom conventional ventilation or HFOV fails. ECMO is most often used before repair of the defect. Several objective criteria for ECMO have been developed. Birthweight and the 5-minute Apgar score may be the best predictors of outcome in patients treated with ECMO. There is no strict lower weight limit for ECMO, but generally, vessels in infants <1,800 g are too small to cannulate.

The duration of ECMO for neonates with diaphragmatic hernia is longer (than for those with isolated PPHN or meconium aspiration and may last up to 2-4 weeks). Timing of repair of the diaphragm while the infant receives ECMO is controversial; some experts prefer early repair to allow a greater duration of ECMO after the repair, whereas many defer repair until the infant has demonstrated the ability to tolerate weaning from ECMO. The recurrence of pulmonary hypertension is associated with high mortality and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, redirection of care toward comfort is usually offered to families.

Prenatal Markers of Severity and Fetal Treatment

The most studied prenatal predictor of outcome in children with CDH studied is fetal US. A prospective study of US at 24-26 weeks compared fetal LHR with mortality. There were no survivors with LHR <1, but all babies with LHR >1.4 survived. A second important consideration is the presence of liver in the thoracic cavity, which is a poor prognostic feature. Because LHR measurements increase with gestation, an O/E LHR is considered a more reliable predictor of severity irrespective of GA. O/E LHR of ≥45% is considered a good prognostic sign, whereas <25% is considered a poor prognostic sign. Fetal MRI is used at many fetal centers at 28-32 weeks for prognostication. The advantages of fetal MRI are that they are operator independent, allow measurement of both lungs, and allow better tissue contrast and better images. Normal reference values for fetal lung volumes on MRI have been published and TLV can be compared with the referent fetus. O/E TLV ≥45% is a good prognostic sign, whereas <25% is considered a poor prognostic sign.

Based on the observation that hydrostatic pressure exerted by fetal lung fluid plays a critical role in lung growth and maturity, a promising fetal therapy is in utero tracheal occlusion **(fetoscopic endoluminal tracheal occlusion [FETO])**. FETO therapy at 27–29 weeks' gestation improves survival from 15% to 40% in fetuses with severe left CDH with O/E LHR of <25%; preterm birth is a risk factor. FETO therapy is only offered at a select few centers across the United States (see Chapter 118).

Surgical Repair

Most experts plan surgery at least 48 hours after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low PIP, and Fio_2 <50%. If the newborn is receiving ECMO, an ability to be weaned from this support should be a consideration before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers the cannulas are removed. A subcostal approach is most frequently used (Fig. 131.3). This allows for good visualization of the defect, and if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (Silastic) patch can be placed, commonly known as a silo. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

The defect size and amount of native diaphragm present are variable. Whenever possible, a primary repair using native tissue is performed. If the defect is too large, a porous polytetrafluoroethylene (Gore-Tex) patch is used.

Following surgical repair, the infant must be carefully monitored for worsening pulmonary hypertension. In some patients, a postoperative course of ECMO is needed. Other recognized complications include bleeding, chylothorax, and bowel obstruction. CDH recurrence can occur in about 10% of cases, usually during the first year of life, but can occur up to the first 5 years of life. There is a higher recurrence rate of CDH in children with patches (the patch does not grow as the child grows) than in those with native tissue repairs, those with larger defects, and those with liver in the defect. A loosely fitted patch may reduce the recurrence rates.

Outcome and Long-Term Survival

Overall survival of liveborn infants with CDH is 75%. Relative predictors of a poor prognosis include an associated major anomaly and syndromes,

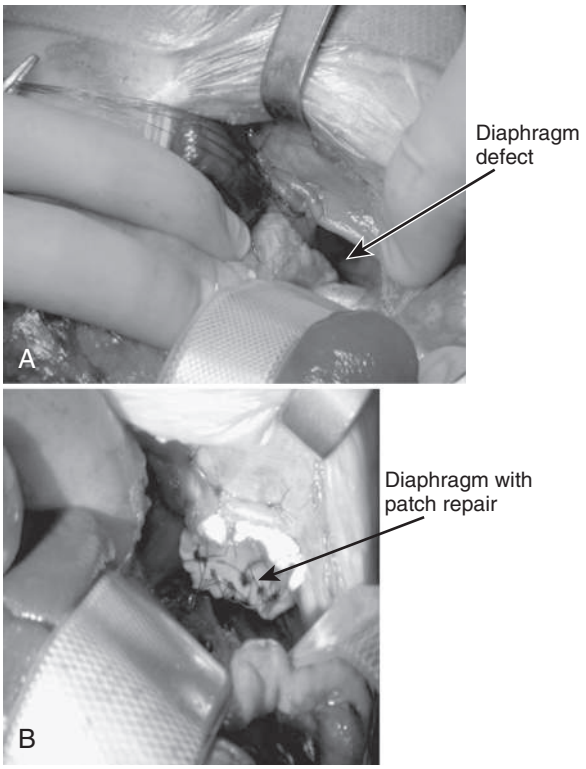

Fig. 131.3 A, Intraoperative photo of congenital diaphragmatic hernia (CDH) before repair. B, Intraoperative photo of patch repair of CDH.

severe pulmonary hypoplasia, herniation to the contralateral lung, and the need for ECMO. The size of the defect appears to be the strongest predictor of morbidity.

Pulmonary problems continue to be a source of morbidity for long-term survivors of CDH. Children receiving CDH repair who were studied at 6-11 years of age demonstrated significant decreases in forced expiratory flow at 50% of vital capacity and decreased peak expiratory flow. Chronic lung disease can occur in about 15% of patients. Both obstructive and restrictive patterns can occur. Those without severe pulmonary hypertension and volutrauma do the best. Those at highest risk include children who required ECMO and patch repair, but the data clearly show that CDH survivors who did not require ECMO also need frequent attention to pulmonary issues. At discharge, up to 20% of infants require oxygen, but only 1–2% require oxygen past 1 year of age.

Gastroesophageal reflux disease (GERD) is reported in >50% of children with CDH. GERD is more common in children whose diaphragmatic defect involves the esophageal hiatus. **Intestinal obstruction** is reported in up to 20% of children and may result from a midgut volvulus, adhesions, or a recurrent hernia that became incarcerated.

Children with CDH typically have delayed growth in the first 2 years of life. Contributing factors include poor intake, GERD, and a caloric requirement that may be higher because of the energy required to breathe. Many children normalize and "catch up" in growth by the time they are 2 years old.

Neurocognitive defects are common and may result from the disease or the interventions. The incidence of neurologic abnormalities is higher in infants who require ECMO (67% vs 24% of those who do not). The abnormalities are similar to those seen in neonates treated with ECMO for other diagnoses and include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in up to 28% of children who underwent ECMO. The majority of neurologic abnormalities are classified as mild to moderate.

Other long-term problems include pectus excavatum and scoliosis. Survivors of CDH repair, particularly those requiring ECMO support, have a variety of long-term abnormalities that appear to improve with time but require close monitoring and multidisciplinary support.

Health-related quality of life (HRQoL) of school-age children born with CDH is overall good and comparable to healthy children, although some children report lower quality of life. The burden of the child's diagnosis on families long-term is also reportedly low. ECMO use is associated with a lower HRQoL in certain domains, as is the need for special education services in school, and chronic respiratory problems.

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131.1 Foramen of Morgagni Hernia

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

Failure of the sternal and crural portions of the diaphragm to meet and fuse produces the foramen of Morgagni hernia. These defects are usually small, with a greater transverse than anteroposterior diameter, and are more often right sided (90%) but may be bilateral. The transverse colon, small intestine, or liver is usually contained in the hernial sac. Most children with these defects are asymptomatic and are diagnosed beyond the neonatal period, often by chest radiograph performed for evaluation of another condition. The anterolateral radiograph shows a structure behind the heart, and a lateral film localizes the mass to the retrosternal area. Chest CT or MRI confirms the diagnosis. When symptoms occur, they can include recurrent respiratory infections, cough, vomiting, or reflux; in rare cases, incarceration may occur. Repair is recommended for all patients, in view of the risk of bowel strangulation, and can be accomplished laparoscopically. Prosthetic material is rarely required.

131.2 Paraesophageal Hernia

Shawn K. Ahlfeld

Paraesophageal hernia is differentiated from the hiatal hernia in that the gastroesophageal junction is in the normal location. The herniation of the stomach alongside or adjacent to the gastroesophageal junction is prone to incarceration with strangulation and perforation. A previous Nissen fundoplication and other diaphragmatic procedures are risk factors. This unusual diaphragmatic hernia should be repaired promptly after identification.

131.3 Eventration

Krishna K. Acharya, Alicia J. Sprecher, and Susan S. Cohen

Eventration of the diaphragm is an abnormal elevation consisting of a thinned diaphragmatic muscle that causes elevation of the entire hemidiaphragm or more often the anterior aspect of the hemidiaphragm. This elevation produces a paradoxical motion of the affected hemidiaphragm. Most eventrations are asymptomatic and do not require repair. A congenital form is the result of either incomplete development of the muscular portion or central tendon or abnormal development of the phrenic nerves. Congenital eventration may affect lung development, but it has not been associated with pulmonary hypoplasia. The differential diagnosis includes diaphragmatic paralysis, diaphragmatic hernia, traction injury, and iatrogenic injury after heart surgery. Eventration is also associated with pulmonary sequestration, congenital heart disease, spinal muscular atrophy with respiratory distress, and chromosomal trisomies. Most eventrations are asymptomatic and do not require repair. The indications for surgery include continued need for mechanical ventilation, recurrent infections, and failure to thrive. Large or symptomatic eventrations can be repaired by plication through an abdominal or thoracic approach that is minimally invasive.

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Chapter 132

Pulmonary Air Leaks: Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Pulmonary air leaks represent air breaching the alveolus and entering potential cavities within the chest. *Asymptomatic* pneumothorax, usually unilateral, is estimated to occur in 1–2% of all newborn infants; *symptomatic* pneumothorax and pneumomediastinum are less common. The incidence of pneumothorax is increased in infants with lung diseases such as meconium aspiration and respiratory distress syndrome (RDS); in those who receive assisted ventilation, especially if high-frequency ventilation (HFV) support is necessary; and in infants with pulmonary hypoplasia.

ETIOLOGY AND PATHOPHYSIOLOGY

The most common cause of pneumothorax is overdistention resulting in alveolar rupture. Alveolar overdistention can occur with positive pressure ventilation during neonatal resuscitation, or it may occur in association with the "ball-valve" phenomenon that results from aspiration (classically meconium) and bronchial/bronchiolar obstruction. Although spontaneous rupture of an underlying pulmonary malformation (e.g., lobar emphysema, congenital lung cyst, pneumatocele) occurs, pneumothorax usually occurs in an otherwise normal lung, and no underlying etiology is identified.

Pneumothorax associated with **pulmonary hypoplasia** is common, tends to occur during the first few hours after birth, and is caused by reduced alveolar surface area and poorly compliant lungs. It is associated with disorders of decreased amniotic fluid volume (Potter syndrome, renal agenesis, renal dysplasia, chronic amniotic fluid leak), decreased fetal breathing movement (oligohydramnios, neuromuscular disease, fetal akinesia syndrome), pulmonary space-occupying lesions (diaphragmatic hernia, pleural effusion, chylothorax), and thoracic abnormalities (thoracic dystrophies).

Gas from a ruptured alveolus escapes into the interstitial spaces of the lung, where it tracks along small conducting airways and dissects along the peribronchial and perivascular connective tissue sheaths to the hilum of the lung **(pulmonary interstitial emphysema, PIE)**. If the volume of escaped air is great enough, it may collect in the mediastinal space (pneumomediastinum) or rupture into the pleural space (pneumothorax), subcutaneous tissue **(subcutaneous emphysema)**, and/or pericardial sac **(pneumopericardium)**.

Tension pneumothorax occurs if an accumulation of air within the pleural space is sufficient to elevate intrapleural pressure above atmospheric pressure. Unilateral **tension pneumothorax** results in impaired ventilation not only in the ipsilateral lung but also in the contralateral lung because of a shift in the mediastinum toward the contralateral side. Compression of the vena cava and torsion of the great vessels may interfere with venous return.

CLINICAL MANIFESTATIONS

The physical findings of a clinically asymptomatic pneumothorax are hyperresonance and diminished ipsilateral breath sounds with or without tachypnea. Symptomatic pneumothorax is characterized by respiratory distress, which varies from merely high respiratory rate to severe dyspnea, tachypnea, and cyanosis. Irritability and restlessness or apnea may be the earliest signs. The onset is usually sudden but may be gradual; an infant may rapidly become critically ill. Physical exam findings include chest asymmetry with an increased anteroposterior diameter, hyperresonance, and diminished or absent breath sounds. The heart is displaced toward the contralateral side, resulting in displacement of the cardiac apex and point of maximal impulse. The diaphragm is displaced downward, as is the liver with right-sided pneumothorax, and may result in abdominal distention. Because pneumothorax may be bilateral in approximately 10% of patients, symmetry of findings does not rule it out. In tension pneumothorax, signs of shock are typical.

Pneumomediastinum can occur with or without a pneumothorax and itself is usually asymptomatic. The degree of respiratory distress depends on the amount of trapped gas; if great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last two findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, **subcutaneous emphysema** in newborn infants is almost pathognomonic of pneumomediastinum. Rarely, air may embolize into the circulation (pulmonary air embolism) and cause cutaneous blanching, air in intravascular catheters, an air-filled heart and vessels on chest radiographs, and death.

PIE may precede the development of a pneumothorax or may occur independently and lead to increasing respiratory distress as a result of decreased compliance, hypercapnia, and hypoxemia. Hypoxemia is caused by an increased $P_A\text{-}aO_2$ gradient and intrapulmonary shunting. Progressive enlargement of blebs of gas may result in cystic dilation and respiratory deterioration resembling pneumothorax. In severe cases, PIE precedes the development of bronchopulmonary dysplasia (BPD). Avoidance of high inspiratory or mean airway pressures may prevent the development of PIE.

Pneumopericardium is generally associated with pneumothorax with air moving into the pericardium via areas of weakness in the pericardiac sac or via embryonic connections between the pleura and pericardium. Pneumopericardium may be asymptomatic, requiring only general supportive treatment, but it usually manifests as sudden shock with tachycardia, muffled heart sounds, and poor pulses suggesting tamponade. Air pressure within the pericardium can cause cardiac tamponade.

Preterm infants whose course is complicated by pulmonary air leaks are at increased risk for mortality, BPD (see Chapter 127), severe intracranial hemorrhage, and prolonged NICU stays.

DIAGNOSIS

Pneumothorax and other air leaks should be suspected in newborn infants who show signs of respiratory distress, are restless or irritable, or have a sudden change in condition. The diagnosis of pneumothorax is established by chest radiography, with the edge of the collapsed lung standing out in relief against the pneumothorax (Fig. 132.1). Pneumomediastinum is signified by hyperlucency around the heart border and between the sternum and the heart border and the displacement of the thymus by air, typically referred to as the "spinnaker sail" sign (Fig. 132.2). *Transillumination* of the thorax is often helpful in the emergency diagnosis of pneumothorax; the affected side transmits excessive light. In pneumopericardium, chest radiography demonstrates a halo of air around the cardiac silhouette. PIE appears as small cystic

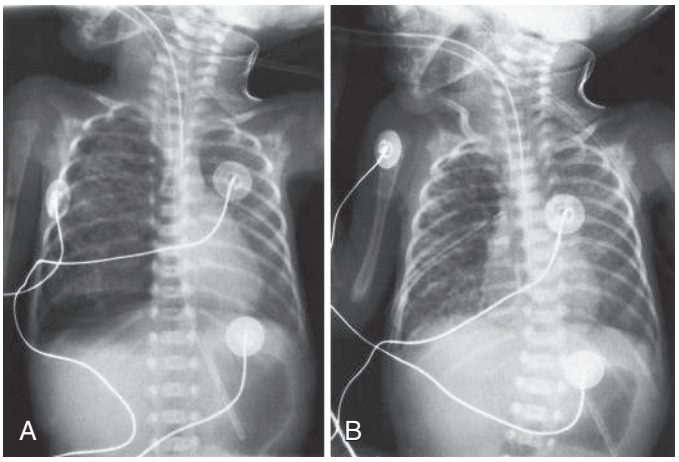

Fig. 132.1 A, Right-sided tension pneumothorax and widespread right lung pulmonary interstitial emphysema (PIE) in a preterm infant receiving intensive care. B, Resolution of pneumothorax with a chest tube in place; PIE persists. *(From Meerstadt PWD, Gyll C. Manual of Neonatal Emergency X-Ray Interpretation. Philadelphia: Saunders; 1994. p. 73.)*

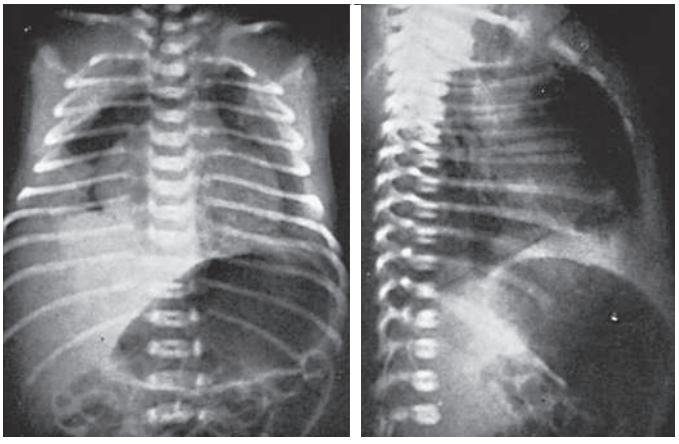

Fig. 132.2 Pneumomediastinum in newborn infant. Anteroposterior view *(left)* demonstrates compression of the lungs, and lateral view *(right)* shows bulging of the sternum, each resulting from distention of the mediastinum by trapped air.

radiolucencies along the interstitium often with hyperexpansion and is typically only seen in premature infants with preexisting lung disease.

PREVENTION

Early recognition of patients at risk for air leak is essential. Infants with oligohydramnios, extreme prematurity, or congenital pulmonary malformations are at increased risk. Surfactant therapy for RDS (see Chapter 126) reduces the incidence of **pneumothorax**. Avoidance of high inspiratory or mean airway pressures may prevent the development of air leaks.

TREATMENT

Without a continued air leak, small asymptomatic and mildly symptomatic pneumothorax, pneumomediastinum, and pneumopericardium require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring ventilatory support. Frequent small feedings may prevent gastric dilation and minimize crying, which can further compromise ventilation and worsen the pneumothorax. Breathing 100% oxygen in term infants may accelerate the resorption of free pleural air into blood by reducing the nitrogen tension in blood and producing a resultant nitrogen pressure gradient from the trapped gas in the blood; however, this is no longer practiced given the risks of oxygen toxicity.

When a pneumothorax is large, expanding, or with severe respiratory or circulatory embarrassment, emergency decompression by needle thoracentesis and/or chest tube placement is indicated. Needle thoracentesis is typically accomplished with the use of an angiocath or a 23-gauge butterfly needle attached to a stopcock and syringe to withdraw air. It can be inserted into the second intercostal space of the anterior chest. After the needle thoracentesis a chest radiograph should be obtained to evaluate and monitor for reaccumulation.

Chest tube placement should be undertaken in cases of recurrent pneumothorax after needle decompression or as a primary intervention in select patients at risk for ongoing air leak (i.e., on high-pressure invasive ventilation). In studies comparing needle decompression with primary chest tube placement there are no differences in mortality; however, approximately 30% of patients receiving a needle thoracentesis eventually required chest tube placement. **Chest tube placement** should occur under sterile conditions whenever possible and be preceded by appropriate analgesia. Pigtail catheters are the preferred type of chest tube in infants because of higher success rates and low complication rates. These catheters are placed using the Seldinger technique by introducing a needle, aspirating free air, and subsequently introducing a guidewire over which a pigtail catheter is advanced. Ideally the chest tube should be introduced into the fourth intercostal space (generally at the level of the nipple) in the anterior axillary line. Following placement, the chest tube should be attached to underwater seal drainage or continuous suction (−5 to −20 cm H_2O). Serial chest radiographs should be obtained for all infants with a chest tube in place.

Pneumopericardium with clinical symptoms (tamponade) requires prompt evacuation of entrapped air via pericardiocentesis. **Pericardiocentesis** should be performed using sterile technique and analgesia whenever possible. Ideally an echocardiogram should be completed before undertaking the procedure and cardiology or cardiothoracic surgery involvement is encouraged. Continuous cardiopulmonary monitoring is essential during the procedure. A 20–23-gauge butterfly needle is introduced into the chest to the left of the subxiphoid process at a 30–45-degree angle pointing toward the right shoulder. The needle is advanced until air returns and the pericardium is subsequently evacuated of air. The provider should stop aspirating once air no longer returns, if there is blood return, or if ectopy is observed. Following the procedure an echocardiogram should be obtained.

Treatment of PIE may include bronchoscopy in patients with evidence of mucous plugging, selective intubation and ventilation of the uninvolved bronchus, oxygen, general respiratory care, and use of HFV.

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Chapter 133

Pulmonary Hemorrhage

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the first 2 weeks of life. The reported incidence at autopsy varies from 1-4 per 1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight (ELBW) infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of respiratory distress syndrome (RDS). The onset may occur at birth or may be delayed several days. **Hemorrhagic pulmonary edema** is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The risk of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, patent ductus arteriosus (PDA), congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication in which the rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1–5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting an additional bleeding diathesis, such as disseminated intravascular coagulation. In preterm infants, often intraventricular hemorrhage can occur at the same time. Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 458).

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and tamponade with increased mean airway pressure (often requiring high-frequency ventilation [HFV]). Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intraalveolar blood and protein can inactivate surfactant.

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Chapter 134

Digestive System Disorders

Robert M. Kliegman

Signs and symptoms suggestive of gastrointestinal (GI) tract pathology in the newborn may reflect immaturity, disorders specific to the GI tract, or systemic diseases affecting the GI tract as part of a multisystem disorder (Table 134.1; see Chapter 121).

Feeding intolerance in the very low birthweight neonate may be due to immaturity of GI motility but also to anatomic lesions from the esophagus to the anus, as well as systemic, metabolic (galactosemia, etc.), or inflammatory processes (sepsis, hemophagocytic lymphohistiocytosis). Recognizing other organ system abnormalities and abnormal laboratory findings (anemia, thrombocytopenia, leukocytosis, neutropenia, elevated inflammatory markers, acidosis, hypoglycemia) may help identify the specific disease.

Table 134.1 Differential Diagnosis of Gastrointestinal Symptoms

SYMPTOM	GI DISORDERS	SYSTEMIC DISORDERS
Emesis	Reflux Volvulus Pyloric stenosis Hirschsprung disease Imperforate anus NEC Meconium plug	Sepsis Inborn error of metabolism Congenital adrenal hyperplasia Increased intracranial pressure
Jaundice	Hepatitis Biliary atresia GALD PFIC Alagille syndrome	Physiologic Hemolysis HLH Sepsis HSV Inborn error of metabolism
Abdominal distention	Feeding intolerance GI obstruction Meconium plug Ileus Meconium ileus NEC Pseudoobstruction Inguinal hernia	Sepsis Hypokalemia Hydronephrosis Ascites Hypermagnesemia

GALD, Gestational alloimmune liver disease; PFIC, progressive familial intrahepatic cholestasis; GI, gastrointestinal; NEC, necrotizing enterocolitis; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus.

Chapter 133

Pulmonary Hemorrhage

Alicia J. Sprecher, Krishna K. Acharya, and Susan S. Cohen

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the first 2 weeks of life. The reported incidence at autopsy varies from 1-4 per 1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight (ELBW) infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of respiratory distress syndrome (RDS). The onset may occur at birth or may be delayed several days. **Hemorrhagic pulmonary edema** is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The risk of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, patent ductus arteriosus (PDA), congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication in which the rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1–5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting an additional bleeding diathesis, such as disseminated intravascular coagulation. In preterm infants, often intraventricular hemorrhage can occur at the same time. Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 458).

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and tamponade with increased mean airway pressure (often requiring high-frequency ventilation [HFV]). Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intraalveolar blood and protein can inactivate surfactant.

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Chapter 134

Digestive System Disorders

Robert M. Kliegman

Signs and symptoms suggestive of gastrointestinal (GI) tract pathology in the newborn may reflect immaturity, disorders specific to the GI tract, or systemic diseases affecting the GI tract as part of a multisystem disorder (Table 134.1; see Chapter 121).

Feeding intolerance in the very low birthweight neonate may be due to immaturity of GI motility but also to anatomic lesions from the esophagus to the anus, as well as systemic, metabolic (galactosemia, etc.), or inflammatory processes (sepsis, hemophagocytic lymphohistiocytosis). Recognizing other organ system abnormalities and abnormal laboratory findings (anemia, thrombocytopenia, leukocytosis, neutropenia, elevated inflammatory markers, acidosis, hypoglycemia) may help identify the specific disease.

Table 134.1 Differential Diagnosis of Gastrointestinal Symptoms

SYMPTOM	GI DISORDERS	SYSTEMIC DISORDERS
Emesis	Reflux Volvulus Pyloric stenosis Hirschsprung disease Imperforate anus NEC Meconium plug	Sepsis Inborn error of metabolism Congenital adrenal hyperplasia Increased intracranial pressure
Jaundice	Hepatitis Biliary atresia GALD PFIC Alagille syndrome	Physiologic Hemolysis HLH Sepsis HSV Inborn error of metabolism
Abdominal distention	Feeding intolerance GI obstruction Meconium plug Ileus Meconium ileus NEC Pseudoobstruction Inguinal hernia	Sepsis Hypokalemia Hydronephrosis Ascites Hypermagnesemia

GALD, Gestational alloimmune liver disease; PFIC, progressive familial intrahepatic cholestasis; GI, gastrointestinal; NEC, necrotizing enterocolitis; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex virus.

Chapter 135

Meconium Ileus, Peritonitis, Intestinal Obstruction, and Gastroschisis

Eric C. Eichenwald

Meconium consists of bile salts, bile acids, and debris shed from the intestinal mucosa in the intrauterine period. More than 90% of full-term newborn infants and 80% of very low birthweight (VLBW) infants pass meconium within the first 24 hours. The possibility of intestinal obstruction should be considered in any infant who does not pass meconium by 24-36 hours.

MECONIUM PLUGS

Meconium plugs syndrome refers to intestinal obstruction, usually in the distal colon, rectum, and anal canal, caused by meconium plugs (Fig. 135.1). Resulting from a disproportionately low amount of water in the intestinal lumen, meconium plugs are a rare cause of intrauterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis (CF). **Anorectal plugs** may also cause mucosal ulceration from bowel wall erosion and subsequent intestinal perforation. **Meconium plugs** are associated with small left colon syndrome in infants of diabetic mothers, infants with CF (40%) and Hirschsprung disease (40%), maternal opiate use, and magnesium sulfate therapy for preeclampsia and tocolysis. Up to 30% of patients can have spontaneous resolution. Initial treatment may include administration of a glycerin suppository or rectal irrigation with isotonic saline. In up to 95% of patients, a Gastrografin enema (meglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 [Tween 80] and 37% organically bound iodine) will be both diagnostic and therapeutic, inducing passage of the plug, presumably because the high osmolarity (1,900 mOsm/L) of the solution draws fluid rapidly into the intestinal lumen and loosens the inspissated material. Such rapid loss of fluid into the bowel may result in acute fluid shifts with dehydration and shock, so it is advisable to dilute the contrast material with an equal amount of water and provide intravenous (IV) fluids, during and for several hours after the procedure, sufficient to maintain normal vital signs, urine output, and electrolytes. After removal of a meconium plug, the infant should be observed closely, and consideration given to performing diagnostic testing to identify **Hirschsprung disease** (congenital aganglionic megacolon; see Chapter 378.4) and CF (see Chapter 454).

MECONIUM ILEUS

Meconium ileus, or impaction of inspissated meconium in the distal small bowel, accounts for up to 30% of cases of neonatal intestinal obstruction. It is common in patients with CF in whom the lack of fetal pancreatic enzymes inhibits digestive mechanisms, and meconium becomes viscid and mucilaginous. Clinically, neonates present with intestinal obstruction with or without perforation. Abdominal distention is prominent, and vomiting, often bilious, becomes persistent, although occasionally inspissated meconium stools may be passed shortly after birth. Meconium ileus can present as early as in utero, in which the fetus develops acute intestinal obstruction resulting in volvulus or perforation, peritoneal ascites, meconium peritonitis, and hydrops; if untreated, fetal loss may occur.

Meconium ileus is primarily associated with cystic fibrosis transmembrane regulator (CFTR) pathologic variants F508del, G542X, W1282X, R553X, and G551D. Patients with two copies of the F508del variant have a 25% chance of presenting with meconium ileus. F508del plus any other CF mutation confers 17% risk, and two other CF variants confer a 12% risk of meconium ileus. In addition, non-CFTR genetic modifier genes influence meconium ileus. In families who already have at least one child with CF complicated by meconium ileus, there is a 39% risk for meconium ileus in subsequent children, which is more than the rates expected with autosomal recessive inheritance. In a twin study, 82% of monozygotic twins showed concordance for meconium ileus, whereas only 22% of dizygotic and 24% of two affected siblings showed concordance. Positive newborn screening for CF should prompt sweat testing when the infant weighs >2 kg and is at least 36 weeks of corrected gestational age. Genetic testing confirms the diagnosis of CF (see Chapter 454). In ~20% of patients with meconium ileus, there is no evidence of CF; in some of these patients, pathogenic variants in *GUCY2C* are identified.

The differential diagnosis involves other causes of intestinal obstruction, including intestinal pseudoobstruction, and other causes of pancreatic insufficiency (see Chapter 398). Prenatal diagnosis is readily achieved by ultrasound with identification of enlarged bowel loops or a mass with distention of the proximal small bowel. Clinically the diagnosis can be made with a history of CF in

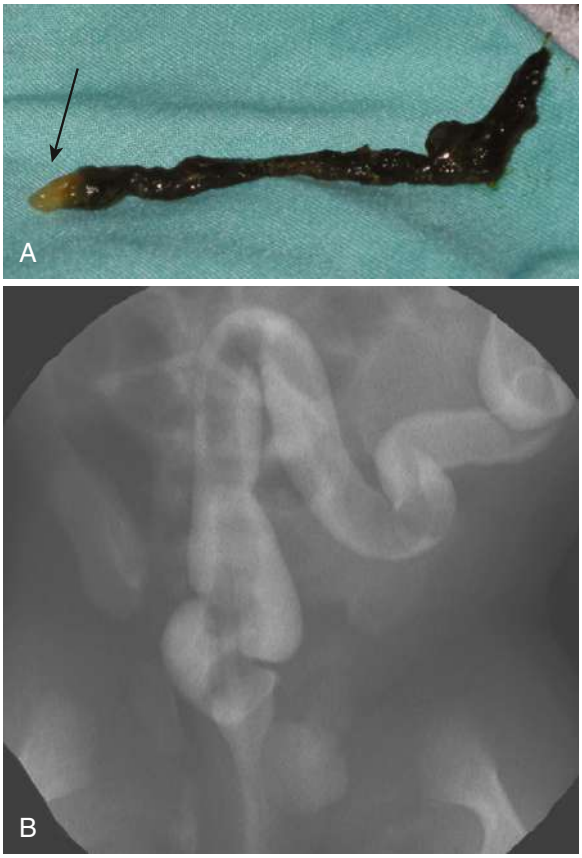
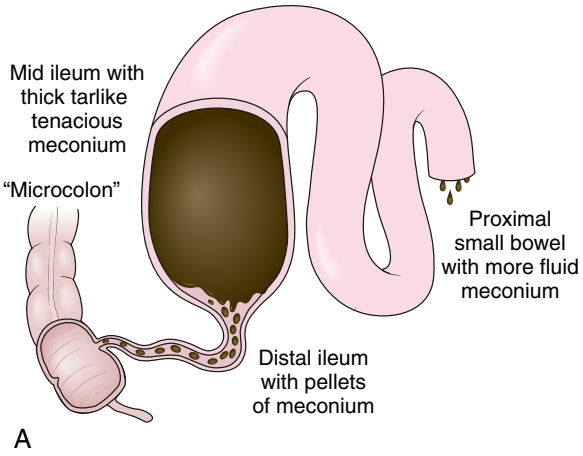


Fig. 135.1 Meconium plug. **A,** Meconium plug evacuated after a diagnostic contrast enema demonstrated the distinctive white tip *(arrow)*. **B,** Image from a contrast enema in a term neonate with vomiting and bowel distension demonstrates the long filling defect characteristic of meconium plug syndrome. The child was relieved of the obstruction after evacuation of the plug, without recurrence of symptoms. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging. 12th ed. Philadelphia: Elsevier; 2013: Fig. 106-14.)*



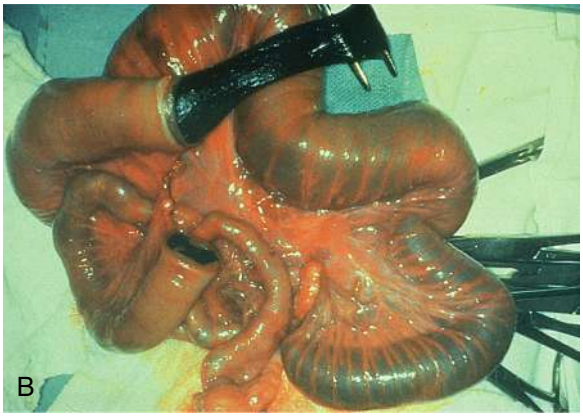


Fig. 135.2 Meconium ileus. **A,** Schematic drawing of uncomplicated meconium ileus. Pellets of inspissated meconium fill the terminal ileum proximal to a microcolon. Several loops of more proximal ileum contain thick, tenacious meconium. **B,** Enterotomy of proximal bowel and the nature of the thick and tenacious meconium. Note the dilated proximal loops of bowel filled with meconium and the progressively small caliber of the distal bowel leading to the microcolon. *(A from Leonidas JC, Berdon WE, et al. Meconium ileus and its complications: a reappraisal of plain film roentgen diagnostic criteria. Am J Roentgenol Radium Ther Nucl Med. 970;108[3]:598–609; B courtesy Dr. Wallace W. Neblett III, Nashville, TN.)*

a sibling, by palpation of doughy or cordlike masses of intestines through the abdominal wall, and from the radiographic appearance. Plain radiographs reveal small bowel obstruction. Air-fluid levels may not be apparent because of the thickened meconium.

In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and are not as evenly filled with gas. At points of heaviest meconium concentration, the infiltrated gas may create a bubbly, granular appearance (Figs. 135.2 and 135.3).

Treatment for simple meconium ileus is a high-osmolarity Gastrografin enema, as described for meconium plugs. If the procedure is unsuccessful or perforation of the bowel wall is suspected, a laparotomy is performed and the ileum opened at the point of largest diameter of the impaction. Approximately 50% of these infants have associated intestinal atresia, stenosis, or volvulus that requires surgery. The inspissated meconium is removed by gentle and patient irrigation with warm isotonic sodium chloride or *N*-acetylcysteine (Mucomyst) solution through a catheter passed between the impaction and

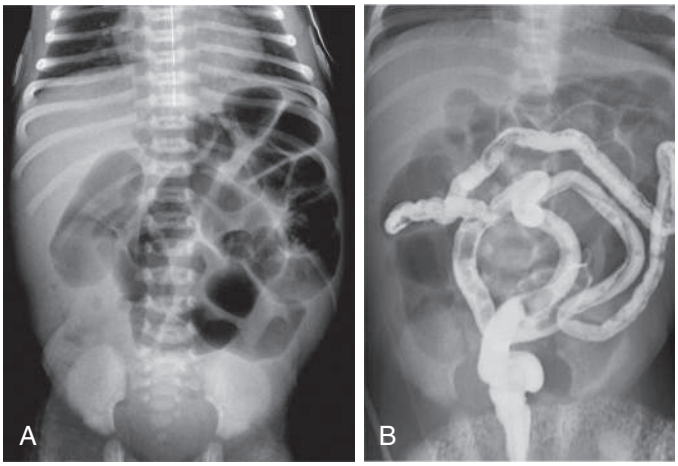


Fig. 135.3 Uncomplicated meconium ileus. **A,** Abdominal radiograph in 3-day-old infant with abdominal distention and bilious aspirates shows dilation of multiple loops of bowel. No calcifications are seen on the radiograph to suggest complicated meconium ileus. Orogastric tube near the gastroesophageal junction was subsequently advanced. **B,** Contrast enema demonstrates a microcolon, with multiple meconium plugs, consistent with the diagnosis of meconium ileus. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging. 13th ed. Philadelphia: Elsevier; 2019: Fig. 102-36)*

the bowel wall. Some patients will require bowel resection with a temporary double-barrel enterostomy followed by serial irrigations and distal refeeding, or primary anastomosis at the initial operation. Most infants with meconium ileus survive the neonatal period. If meconium ileus is associated with CF, the long-term prognosis depends on the severity of the underlying disease (see Chapter 454). In ~20% of patients with meconium ileus, there is no evidence of CF; in some of these patients pathogenic variants in *GUCY2C* are identified.

MECONIUM PERITONITIS

Perforation of the intestine may occur in utero or shortly after birth. Frequently, the intestinal perforation seals naturally with relatively little meconium leakage into the peritoneal cavity. Perforations occur most often as a complication of meconium ileus in infants with CF but occasionally result from a meconium plug or in utero intestinal obstruction of another cause.

Cases at the most severe end of the spectrum may be diagnosed on prenatal ultrasound with fetal ascites, polyhydramnios, bowel dilation, intraabdominal speckled calcifications, and hydrops fetalis (Fig. 135.4). At the other end are cases in which an intestinal perforation may seal spontaneously and patients remain asymptomatic, except when meconium becomes calcified and is later discovered on radiographs. Alternatively, the clinical picture may be dominated by signs of intestinal obstruction (as in meconium ileus) with abdominal distention, vomiting, and absence of stools or chemical peritonitis presenting with sepsis. Treatment consists primarily of elimination of the intestinal obstruction and drainage of the peritoneal cavity with a timely surgical intervention proved to result in high survival rate and favorable outcome even in complicated meconium peritonitis.

GASTROSCHISIS

Gastroschisis is the herniation of abdominal contents (usually small intestine) through a defect in the anterior abdominal wall lateral to the umbilical cord (Fig. 135.5). The etiology is unknown, but it has been

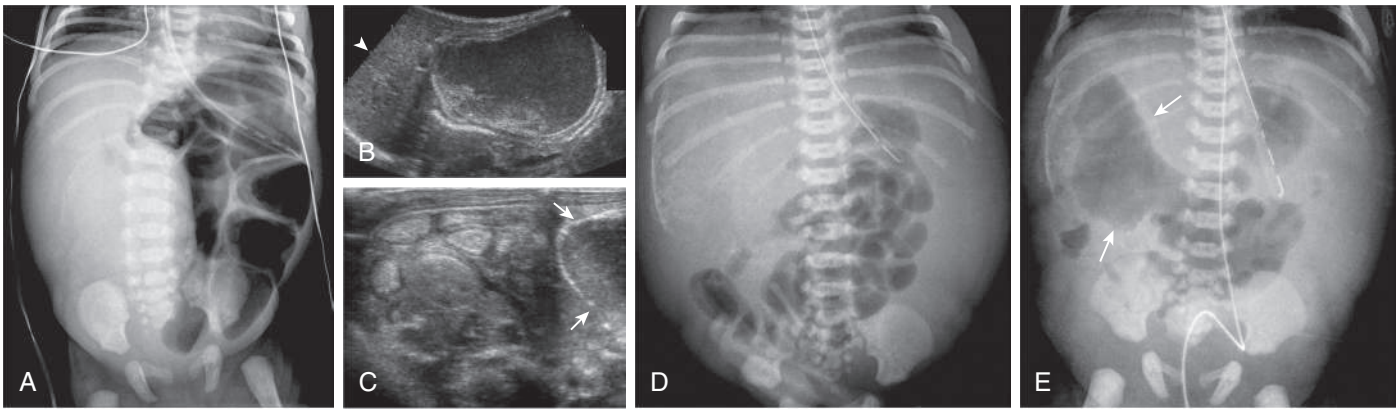


Fig. 135.4 Complicated meconium ileus. **A,** Abdominal radiograph in 2-day-old girl with abdominal distention and bilious aspirates shows absence of bowel gas in the right abdomen with a partly calcified mass displacing gas-filled dilated loops of bowel to the left. **B,** Ultrasound image demonstrates the subhepatic, partly calcified mass with internal debris and fluid-fluid level *(arrowhead)*. **C,** Additional ultrasound image shows a portion of the cyst wall *(arrows)* and multiple, abnormal, hyperechoic loops of bowel. **D,** Abdominal radiograph in different 1-day-old infant shows a calcified mass in right upper quadrant, shown at sonography to represent a loculated complex meconium collection. **E,** Radiograph a few hours later of the same infant shown in **D** shows a persistent perforation with gas entering into the right upper quadrant collection *(arrows)*. *(From Hernanz-Schulman M. Congenital and neonatal disorders. In Coley BD, ed. Caffey's Pediatric Diagnostic Imaging. 13th ed. Philadelphia: Elsevier; 2019: Fig. 102-37)*

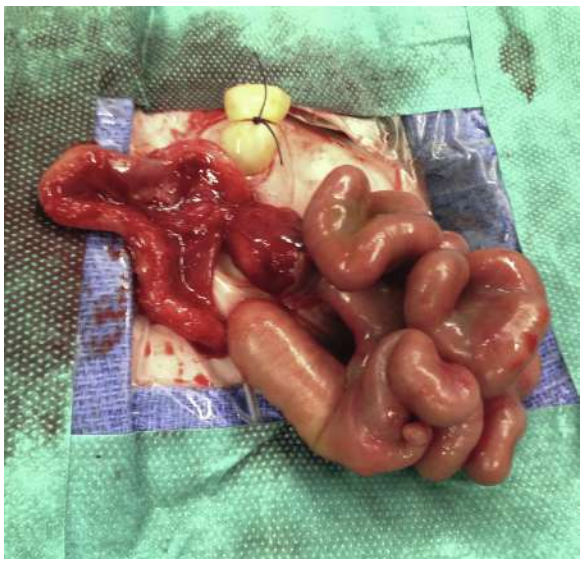


Fig. 135.5 Intraoperative view of a complex gastroschisis with intestinal atresia. Note the severe bowel matting in the complex gastroschisis. *(Modified from Vinit N, Talbotec C, De Tristan MA, et al. Predicting factors of protracted intestinal failure in children with gastroschisis. J Pediatr. 2022;243:122–129. Fig. 1B.)*

associated with young maternal age and possible opioid use; the incidence is ~2-5 infants in 10,000 births.

Gastroschisis is usually an isolated anomaly but has a high morbidity and mortality especially in complex lesions associated with intestinal atresias and necrosis resulting in short bowel syndrome and intestinal failure (see Chapter 385.6). Treatment requires resection of atretic or necrotic tissue and long-term parenteral alimentation until enteral nutrition can be established.

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Chapter 136

Necrotizing Enterocolitis

Sagori Mukhopadhyay and Misty Good

Necrotizing enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal (GI) tract in the newborn period. The disease is characterized by various degrees of mucosal or transmural necrosis of the intestine followed by local and systemic inflammation. The cause of NEC remains unclear but is most likely multifactorial.

DEFINITION

NEC is clinically identified using a combination of clinical and radiographic signs and staged by categorizing NEC into suspected (stage I), definite (stage II, clinical signs of abdominal pathology with an abnormal abdominal radiograph showing pneumatosis intestinalis, portal venous gas, or ileus), and advanced (stage III, signs of stage II plus severe systemic signs of inflammation and acidosis with or without signs of intestinal perforation). In addition, NEC is also categorized into *medical and surgical NEC* defined by the type of acute intervention required. These criteria have been criticized for categorizing conditions with heterogeneous origins as the same disease. For example, conditions such as spontaneous intestinal perforation, septic ileus, and allergic enterocolitis can present with signs similar to NEC, but they arise from differing pathogenesis and may have differing outcomes. Similarly, term infants often present with NEC attributable to coexisting conditions such as congenital heart disease or gastroschisis, and likely do not share identical pathogenesis with NEC occurring in preterm infants. To minimize the heterogeneity of presentations that get diagnosed as NEC, a definition of "preterm NEC" has been proposed for use in clinical research. **Preterm NEC** in clinical research is defined by the presence of (1) clinical sign of abdominal distention and/or hematochezia; (2) onset between 10 days after birth to 36 weeks' postmenstrual age with the highest risk period being 30-32 weeks'

postmenstrual age; and (3) one of the following—pneumatosis intestinalis or portal venous gas by radiograph or ultrasound, histopathologic evidence of intestinal necrosis, or evidence of vasculitis, coagulopathy, or inflammation in the absence of infection.

EPIDEMIOLOGY

Epidemiologic studies have reported changes in NEC incidence in the past decade. Among 473,895 very low birthweight infants (VLBW, birthweight <1,500 g) admitted to one of 820 centers in the United States (2006-2017), the overall rate of NEC was 7.6%. From 2006–2017, there was a significant reduction in the prevalence of medical but not surgical NEC; mortality with NEC also decreased from 20.7% to16.8% among infants with medical NEC, and 36.6% to 31.6% for neonates with surgical NEC.

PATHOLOGY AND PATHOGENESIS

Many factors contribute to the development of the pathologic findings of NEC, including mucosal ischemia and subsequent necrosis; gas accumulation in the submucosa of the bowel wall **(pneumatosis intestinalis)**; and progression of the necrosis to perforation, peritonitis, sepsis, and death. An overview of common hypothesized pathogenic mechanisms, related clinical presentation, and management is shown in Figure 136.1. The distal part of the ileum and the proximal segment of the colon are involved most frequently; in fatal cases, transmural necrosis may extend from the stomach to the rectum **(NEC totalis)**. The pathogenesis of NEC is not fully understood, but three major risk factors have been implicated: prematurity, bacterial colonization of the gut, and enteral feeding. NEC develops primarily in premature infants with exposure to a nutritional substrate in the context of immature intestinal motility, and immunity, microbial dysbiosis, and mucosal ischemia. An underlying genetic predisposition is recognized with variants in genes regulating immunomodulation and inflammation (e.g., toll-like receptor-4, interleukin [IL]-4 receptor α chain, IL-6), apoptosis and cellular repair (e.g., platelet-activating factor), and oxidant stress (e.g., vascular endothelial growth factor, arginine, nitric oxide). *The greatest risk factor for NEC is prematurity, with a mean onset between 30 and 32 weeks' postmenstrual age.* Other risk factors include small for gestational age, polycythemia, and conditions resulting in in utero hypoxia. NEC rarely occurs before the initiation of enteral feeding and is much less common in infants fed human milk.

CLINICAL MANIFESTATIONS

Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset (Table 136.1). Age of onset is inversely related to gestational age. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to GI pathology, such as abdominal tenderness and distention, feeding intolerance, and bloody stools. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Laboratory findings may include neutropenia, anemia, thrombocytopenia, coagulopathy, and metabolic acidosis. Hypotension and respiratory failure are common. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hours.

DIAGNOSIS

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of pneumatosis intestinalis confirms the clinical suspicion of NEC and is diagnostic; 50–75% of patients have pneumatosis when treatment is started (Fig. 136.2). Portal venous gas is a sign of severe disease, and pneumoperitoneum indicates a perforation (Figs. 136.3 and 136.4). Ultrasound may be useful to evaluate for free fluid, abscess, pneumatosis intestinalis, and bowel wall thickness, peristalsis, and perfusion (Fig. 136.5). Doppler flowmetry studies can be used to assess flow in superior mesenteric artery and portal vein.

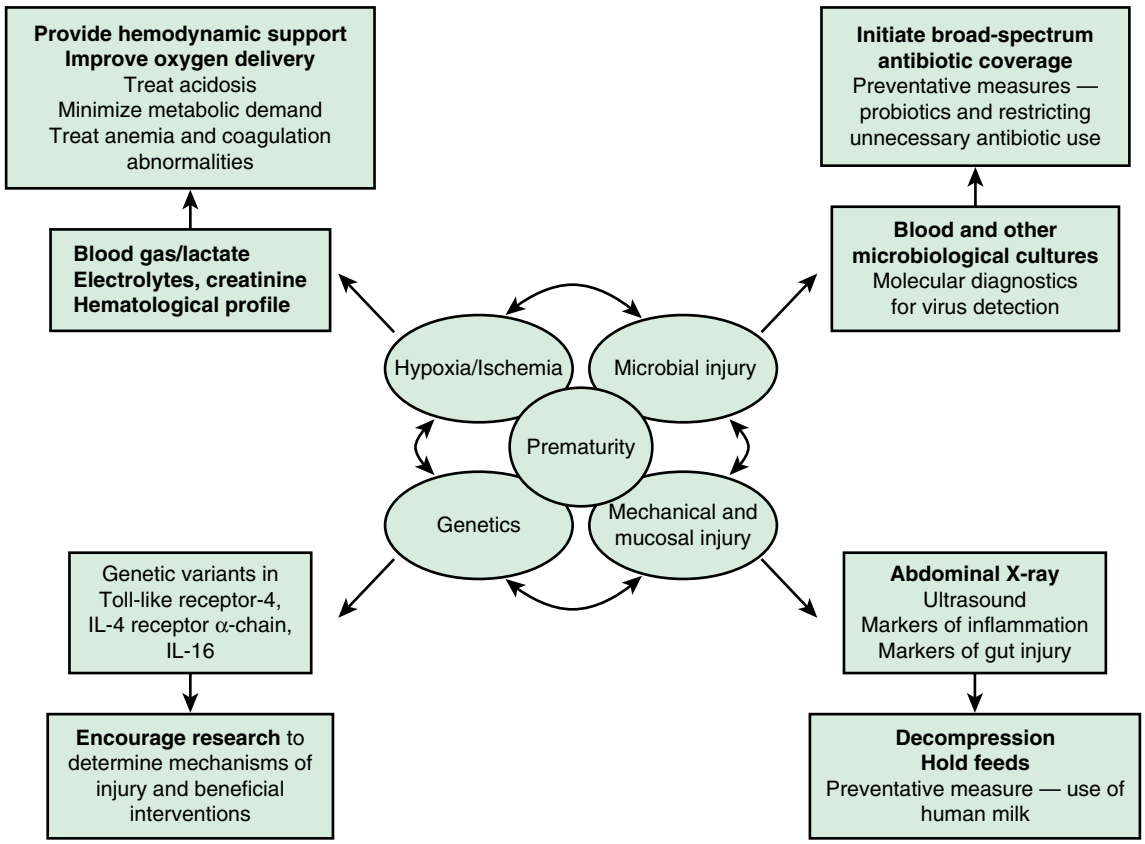

Fig. 136.1 Overview of risk factors and mechanisms of injury in necrotizing enterocolitis–associated presentation and management approaches. **Bold** indicates interventions that are common first-line interventions for NEC. IL, Interleukin. (*Figure created by authors using BioRender.com.*)

Table 136.1 Signs and Symptoms Associated with Necrotizing Enterocolitis

GASTROINTESTINAL	SYSTEMIC
Abdominal distention	Lethargy
Abdominal tenderness	Apnea/respiratory distress
Feeding intolerance	Temperature instability
Delayed gastric emptying	Acidosis (metabolic and/or respiratory)
Emesis	Glucose instability
Occult/gross blood in stool	Poor perfusion/shock
Change in stool pattern/diarrhea	Thrombocytopenia
Abdominal mass	Disseminated intravascular coagulopathy
Erythema of abdominal wall	

From Kanto WP Jr, Hunter JE, Stoll BJ. Recognition and medical management of necrotizing enterocolitis. *Clin Perinatol.* 1994;21:335–346.

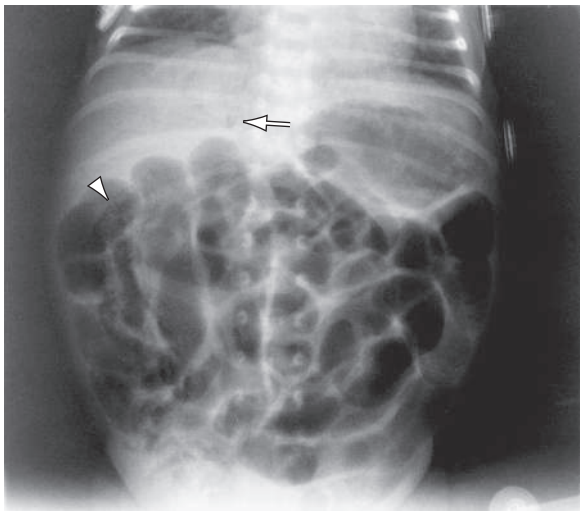

Fig. 136.2 Necrotizing enterocolitis (NEC). Kidney-ureter-bladder film demonstrates abdominal distention, hepatic portal venous gas *(arrow),* and a bubbly appearance of pneumatosis intestinalis (*arrowhead;* right lower quadrant). The latter two signs are thought to be pathognomonic for neonatal NEC.

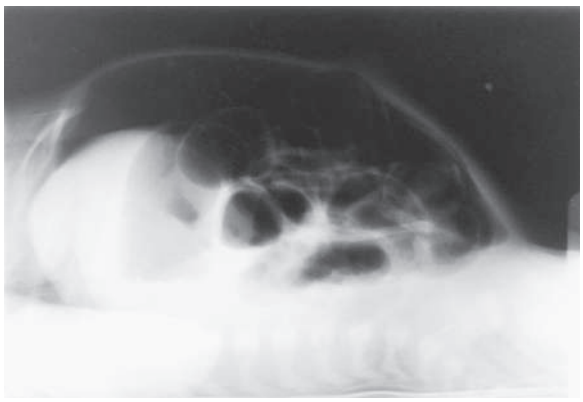

Fig. 136.3 Intestinal perforation. Cross-table abdominal radiograph in patient with neonatal necrotizing enterocolitis demonstrates marked distention and massive pneumoperitoneum, as evidenced by the free air below the anterior abdominal wall.

The differential diagnosis of NEC includes septic ileus, GI obstruction, volvulus, and isolated intestinal perforation. **Idiopathic focal intestinal perforation** can occur spontaneously or can be associated with the early use of postnatal corticosteroids and indomethacin. Pneumoperitoneum develops in such patients, but they are usually less ill than those with NEC. Occasional clusters of NEC cases have been attributed to viral infections, specifically norovirus, enterovirus, and rotavirus. Stool viral testing and infectious disease consultation should be considered when multiple cases occur together.

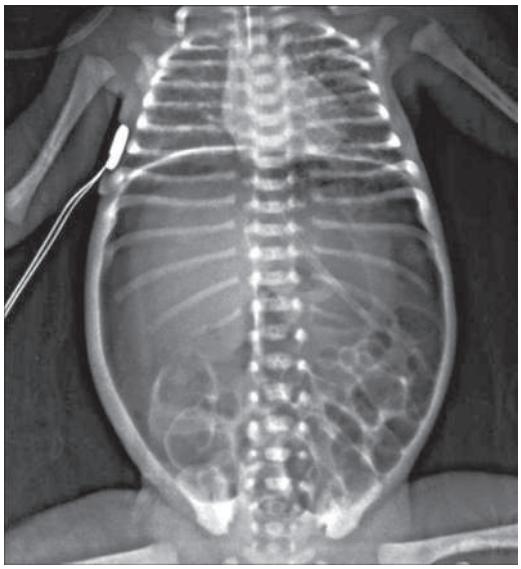

Fig. 136.4 Necrotizing enterocolitis (NEC). Plain abdominal x-ray film of an infant with perforated NEC showing pneumoperitoneum. *(From Tam PKH, Chung PHY, St Peter SD, et al. Advances in paediatric gastroenterology. Lancet. 2017;390:1072–1082. Fig. 4)*

TREATMENT

Rapid initiation of therapy is required for infants with suspected, as well as proven NEC. There is no specific treatment for established NEC, so therapy is directed at providing supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids and antibiotics (see Fig. 136.1). Careful attention to the respiratory status, coagulation profile, and acid-base and electrolyte balances are important. Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC. Umbilical arterial catheters are reported to reduce blood flow in the mesenteric blood vessels and should be removed if they remain in place after a diagnosis of NEC. Maintaining reliable intravenous access for ongoing hemodynamic support and medication administration is critical.

Approximately 16% of definite NEC cases may be associated with bacteremia detected within 72 hours of its diagnosis, most frequently with a gram-negative organism. NEC with associated bacteremia has a higher risk for requiring surgical intervention and mortality. Once blood has been drawn for culture, systemic antibiotics (with broad coverage based on the antibiotic sensitivity patterns in the particular neonatal ICU) should be started immediately. The addition of anaerobic coverage with antibiotics such as metronidazole or clindamycin is variably practiced. Management of NEC with anaerobic coverage is

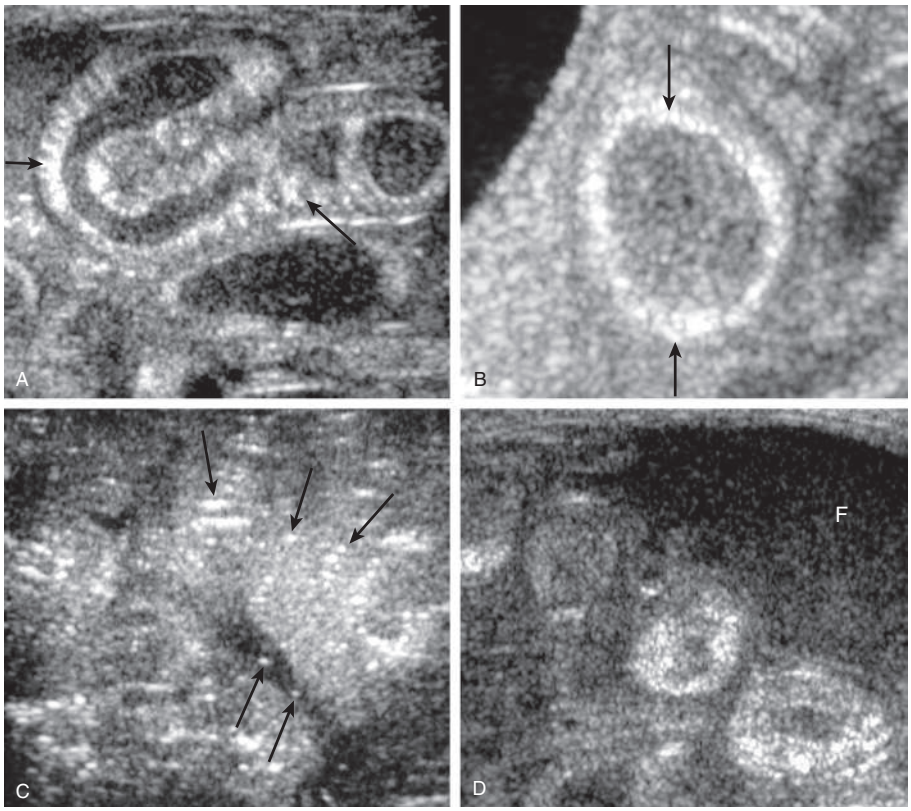

Fig. 136.5 Necrotizing enterocolitis. **A,** Mucosal and submucosal thickening *(arrows)*. **B,** Intramural gas (pneumatosis intestinalis) creates an echogenic ring *(arrows)*. **C,** Widespread echogenic bubbles of gas in the portal veins *(arrows)*. **D,** Fluid with echogenic debris (F) lies adjacent to thick loops. *(From John SD, Hollingsworth C: The pediatric gastrointestinal tract. In Levine D, Rumack CM, Wilson SR, Charboneau JW, eds. Diagnostic Ultrasound, 4th ed. Philadelphia: Elsevier, 2014. Fig 55.29.)*

associated with slightly lower risk of mortality and higher risk of subsequent strictures.

The patient's course should be monitored closely by means of frequent physical assessments in the NICU; sequential anteroposterior and cross-table lateral or lateral decubitus abdominal radiographs to detect intestinal perforation; and serial determinations of hematologic, electrolyte, and acid-base status. A surgeon should be consulted early in the course of treatment. The only *absolute* indication for surgery is evidence of perforation on an abdominal radiograph (pneumoperitoneum). However, this is present in less than half of infants with perforation or necrosis at operative exploration. Progressive clinical deterioration despite maximum medical management, a single fixed bowel loop on serial radiographs, and abdominal wall erythema are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur. The optimal surgical approach, however, remains controversial. The options for surgical treatment include primary peritoneal drainage (PPD) or exploratory laparotomy with resection of the necrotic intestine and usually stoma creation. Laparotomy is usually the initial therapy in the majority of VLBW infants with surgical NEC, even in those <1,000 g. Randomized clinical trials comparing these approaches failed to demonstrate significant differences in survival, nutritional outcomes, or length of stay. However, among those with a diagnosis of NEC *(as opposed to intestinal perforation)*, 69% died or had neurodevelopmental impairment (NDI) when managed with initial laparotomy versus 85% when managed with PPD. In contrast, among infants with a diagnosis of *intestinal perforation*, death or NDI occurred 69% and 63% after initial management with laparotomy or PPD, respectively. When the diagnosis is confirmed NEC, initial management with laparotomy is more likely to reduce risk of death or NDI compared to PPD. However, the ultimate surgical approach for an individual case also depends on the surgeon's assessment and physiologic status of the patient.

PROGNOSIS

In patients with pneumatosis intestinalis at NEC diagnosis, disease progression is nonresponsive to medical management alone in approximately 20–40%; of these that require surgery, 20–50% die. Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include intestinal strictures, which occur in approximately 25–35% of surgically or medically managed patients. After massive intestinal resection, complications from postoperative NEC include short bowel syndrome (malabsorption, growth failure, malnutrition), complications related to central venous catheters (sepsis, thrombosis), and cholestatic jaundice. Preterm infants with NEC who require surgical intervention are at increased risk for adverse growth and neurodevelopmental outcomes.

PREVENTION

The most effective preventive strategy for NEC is the use of human milk (maternal or donor); newborns exclusively fed breast milk have a reduced risk of NEC. However, because human milk does not provide complete nutritional support for very preterm infants, nutritional fortification is usual practice. Some studies have suggested that an "exclusive human milk diet" using human rather than bovine fortifiers may further reduce the risk of NEC. An optimal feeding protocol (rapid vs slow volume increments) has not been discovered; it is important to note that strict adherence to a NICU-specific feeding protocol reduces the risk of NEC. Additionally, while extensive data and meta-analyses would support the use of probiotics to prevent NEC, there is no clear consensus on the safest, most effective formulation, timing of administration, or length of therapy. Other preventive strategies using prebiotics and synbiotics have also been studied, with variable outcomes. Inhibitors of gastric acid secretion (H_2-receptor blockers, proton pump inhibitors), high osmolality enteral fluids, or prolonged empirical antibiotics in the early neonatal period have been associated with increased risk of NEC and should be avoided.

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Chapter 137

Jaundice and Hyperbilirubinemia in the Newborn

Kelsey S. Ryan and Robert M. Kliegman

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. **Jaundice** is observed during the first week after birth in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated **indirect-acting** by nature of the van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin **(direct-reacting).** Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates potentially serious hepatic disorders or a systemic illness.

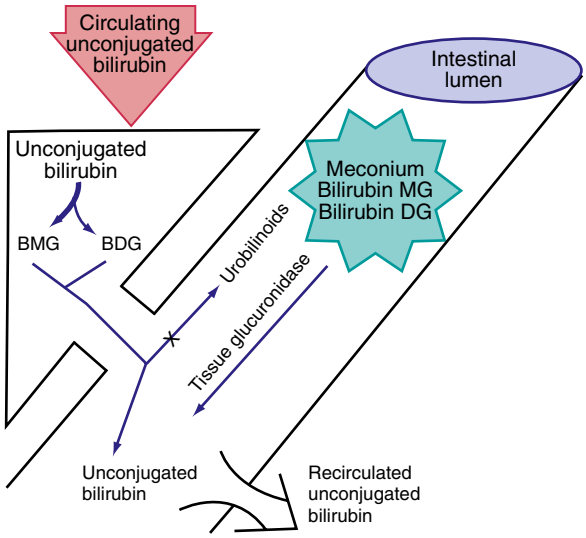

Fig. 137.1 Metabolism of bilirubin in the neonatal period. Neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione *S*-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

ETIOLOGY

During the neonatal period, metabolism of bilirubin is in transition from the *fetal stage,* during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the *adult stage,* during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. **Unconjugated hyperbilirubinemia** may be caused or increased by any factor that (1) increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened RBC life as a result of immaturity or transfusion of cells, increased enterohepatic circulation, infection), (2) damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency), (3) competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation), or (4) leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, prematurity). Gene polymorphisms in the hepatic uridine diphosphate glucuronosyltransferase isoenzyme 1A1 *(UGT1A1)* and the solute carrier organic anion transporter 1B1 *(SLCO1B1)*, alone or in combination, influence the incidence of neonatal hyperbilirubinemia.

The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood-brain barrier (BBB) and nerve cell membranes but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas suboptimal feedings and dehydration increases serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 137.1). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia.

CLINICAL MANIFESTATIONS

Jaundice usually appears during the early neonatal period, depending on etiology. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, approximately 5 mg/dL; mid-abdomen, 15 mg/dL; soles, 20 mg/dL), *but clinical examination cannot reliably estimate serum levels*. Noninvasive techniques for transcutaneous measurement of bilirubin that correlate with serum levels may be used to *screen* infants, but determination of the serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for hemolysis or sepsis. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without treatment, can progress to acute bilirubin encephalopathy (kernicterus) (see Chapter 137.1).

DIFFERENTIAL DIAGNOSIS

The distinction between *physiologic* and *pathologic* jaundice relates to the timing, rate of rise, and extent of hyperbilirubinemia, because some of the same causes of physiologic jaundice (e.g., large RBC mass, decreased capacity for bilirubin conjugation, increased enterohepatic circulation) can also result in pathologic jaundice. Evaluation should be determined on risk factors, clinical appearance, and severity of the hyperbilirubinemia (Tables 137.1-137.3). Jaundice that is present at birth or appears within the first 24 hours after birth should be considered **pathologic** and requires immediate attention. Potential diagnoses would include erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital

Table 137.1 Risk Factors for Severe Neonatal Hyperbilirubinemia

GENETIC FACTORS
- Gilbert syndrome
- Crigler-Najjar syndrome
- Alagille syndrome
- β thalassemia
- Glucose-6-phosphate dehydrogenase deficiency
- Bilirubin glucuronosyltransferase polymorphism
- Pyruvate kinase deficiency
- Erythrocyte structural defects (including hereditary spherocytosis and elliptocytosis)
- Galactosemia

MATERNAL FACTORS
- Family history of severe jaundice, splenectomy, or cholecystectomy
- Primiparity
- Teenage pregnancy
- Diabetes
- Rhesus incompatibility
- ABO incompatibility
- Other blood group isoimmunization
- Use of drugs during labor (including oxytocin, promethazine, and bupivacaine)
- Exclusive breastfeeding

PERINATAL FACTORS
- Mode of deliver (breech vs vertex, instrumentation)
- Birth trauma (cephalohematoma or substantial bruising, extravasation)
- Birth asphyxia
- Congenital infections (including cytomegalovirus and syphilis)
- Sepsis

NEONATAL FACTORS
- Male sex
- Prematurity or low birthweight and small-for-gestational age
- Hypothyroidism
- Polycythemia
- Hypoglycemia
- Low intake of breast milk, dehydration, or weight loss
- Breast milk jaundice
- Jaundice in the first day of life
- Trisomy 21
- Infant of diabetic mother
- Cephalohematoma, other bruising

OTHER RISK FACTORS AND MARKERS
- Previous sibling received phototherapy or exchange transfusion
- Predischarge total serum bilirubin or transcutaneous bilirubin concentration in the high zone
- Use of hemolytic agents (e.g., naphthalene or menthol-based products) in glucose-6-phosphate dehydrogenase deficient population groups
- Folate deficiency
- Aflatoxins
- Hypothermia
- Birth outside of a healthcare facility

Modified from Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. *Lancet Child Adolesc.* 2018;2:610–618. Panel 2, p. 612.

Table 137.2 Evaluation of the Neonate with Significant Jaundice

CONCERN	POSSIBLE DIAGNOSIS	INITIAL LABORATORY TESTS
Jaundice on day 1	Hemolysis* TORCH/sepsis Hepatic failure syndromes† Internal hemorrhage	CBC, smear Total and direct bilirubin Blood type and Coombs test
Jaundice requiring phototherapy	Hemolysis* TORCH/sepsis	As above
Direct/conjugated hyperbilirubinemia	TORCH/sepsis Biliary atresia Other causes of cholestasis‡ Hepatic failure syndromes†	Hepatic enzymes, INR, check newborn screen for metabolic disease, blood glucose, blood ammonia and lactate, urine and blood cultures, CMV and HSV PCR

*Hemolysis may be immune or nonimmune (RBC membrane or enzyme defects).
†Hepatic failure syndromes: HSV, CMV, gestational alloimmune liver disease, mitochondrial liver disease, familial hemophagocytic syndrome.
‡See Chapter 404.
CMV, Cytomegalovirus; CBC, complete blood count; HSV, herpes simplex virus; PCR, polymerase chain reaction; INR, international normalized ratio; TORCH, toxoplasmosis, other, rubella, CMV, herpes.

infections, including syphilis, cytomegalovirus (CMV), rubella, and toxoplasmosis. Significant hemolysis is suggested by a rapid rise in serum bilirubin concentration (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history. An unusually high proportion of direct-reacting bilirubin may characterize jaundice in infants who have received intrauterine transfusions for erythroblastosis fetalis. Jaundice that first appears on the second or third day is usually **physiologic** but may represent a more severe form. Familial nonhemolytic icterus **(Crigler-Najjar syndrome)** and early-onset breastfeeding (suboptimal intake) jaundice are seen initially on the second or third day. Jaundice *appearing* after the third day and within the first week suggests bacterial sepsis or urinary tract infection; it may also be caused by other infections, notably syphilis, toxoplasmosis, CMV, herpes simplex virus (HSV), and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the first day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

There is a long differential diagnosis for jaundice first recognized *after* the first week of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, cystic fibrosis (CF), pyloric stenosis, and congenital hemolytic anemia crises related to RBC morphology and enzyme deficiencies (Fig. 137.2). The differential diagnosis for persistent jaundice during the first month of life includes hyperalimentation-associated cholestasis, hepatitis, CMV, syphilis, toxoplasmosis, familial nonhemolytic icterus, biliary atresia, galactosemia and other inborn errors of metabolism, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

Regardless of gestation or time of appearance of jaundice, patients with *significant* hyperbilirubinemia *and* those with symptoms or signs require a complete diagnostic evaluation, which includes review of risks (Table 137.1), determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, direct antiglobulin/antibody test (DAT) (Coombs test), and examination of a peripheral blood smear. Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of RBC destruction suggest hemolysis (see Table 137.2). In the absence of blood group incompatibility, non–immunologically-induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 137.2). If direct hyperbilirubinemia is present, diagnostic possibilities include hepatitis, congenital bile duct disorders (biliary atresia, paucity of bile ducts, Byler disease), cholestasis, inborn errors of metabolism, CF, congenital hemosiderosis, sepsis, and neonatal hepatic failure syndromes (Table 137.4).

Table 137.3 Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	COMMENTS
		APPEARS	DISAPPEARS	MG/DL	AGE IN DAYS		
"Physiologic jaundice"							Usually relates to degree of maturity
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia caused by metabolic factors							Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Full-term	Indirect	2-3 days	Variable	>12	First wk	<5	Hormonal influences: hypothyroidism, hormones, Gilbert syndrome
Premature	Indirect	3-4 days	Variable	>15	First wk	<5	Genetic factors: Crigler-Najjar syndrome, Gilbert syndrome
Hemolytic states and hematoma	Indirect	May appear in first 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drug: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and hepatoxic factors	Indirect and direct	May appear in first 24 hr	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis, pyelonephritis, hepatitis, toxoplasmosis CMV HSV Rubella, syphilis
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by second wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis, infection, hepatic failure syndromes*

*Gestational alloimmune liver disease, hemophagocytic lymphocytosis, mitochondrial hepatic disorders, inborn errors of metabolism
CMV, Cytomegalovirus; HSV, herpes simplex virus.
From Brown AK. Neonatal jaundice. Pediatr *Clin North Am.* 1962;9:575–603.

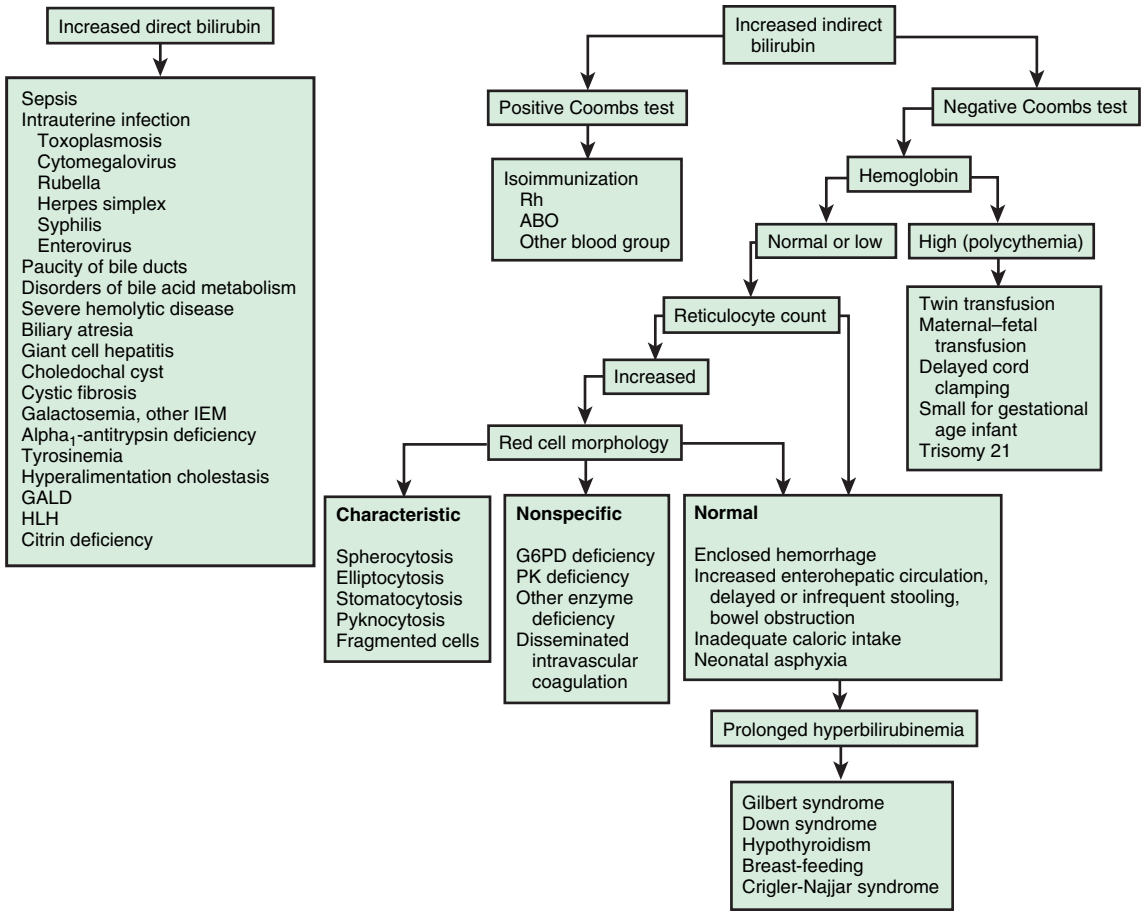

Fig. 137.2 Algorithmic approach to the diagnosis of neonatal jaundice. G6PD, Glucose-6-phosphate dehydrogenase; GALD, gestational alloimmune liver disease; HLH, hemophagocytic lymphohistiocytosis; IDM, infants of diabetic mothers; IEM, inborn error of metabolism; PK, pyruvate kinase. *(From Oski FA. Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, eds. Schaffer and Avery's Diseases of the Newborn. 6th ed. Philadelphia: Saunders; 1991.)*

Table 137.4 Typical Laboratory Findings in Neonatal Liver Failure

	GALD	HLH	MITOCHONDRIAL	VIRAL	ISCHEMIC
Transaminase levels (IU/L)	Normal/mild increase <100	Moderate/significant increase (>1,000)	Moderate increase (100-500)	Significant increase (>1,000)	Significant increase (>1,000-6,000)
INR	Significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase	Moderate/significant increase
Ferritin level (ng/mL)	800-7,000	Significant increase (>20,000)	Variable	Significant increase (>20,000)	Variable depending on underlying cause of ischemia
Triglyceride levels	Normal	Increased	Normal	Normal	Normal
Hypoglycemia	Yes	Often	Yes	Often	Variable
Lactic acidosis	Normal	Normal	Increased	Normal	Often
α-Fetoprotein level (for age)	Increased	Normal	Normal/increased	Normal	Normal
Cholestasis	Progressive after birth	Moderate/significant	Moderate	None/mild at presentation	Mild/moderate

HLH, Hemophagocytic lymphohistiocytosis; GALD, gestational alloimmune liver disease; INR, international normalized ratio.
From Larson-Nath C, Vitola BE. Neonatal acute liver failure. *Clin Perinatol*. 2020;47:25–39. Table 2 with data from Sundaram SS, Alonso EM, Narkewicz, MR, et al. *J Pediatr* 2011;159:813–818; Taylor SA, Whitington, PF. *Liver Transpl*. 2016;22(5):677–685; Bitar R, Thwaites R, Davison S, et al. *J Pediatr Gastroenterol Nutr*. 2017;64(1):70–75; Fellman V, Kotarsky H. *Semin Fetal Neonatal Med*. 2011;16(4):222–228.

PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus jaundice becomes visible on the second or third day, usually peaking between the second and fourth days at 5-6 mg/dL and decreasing to <2 mg/dL between the fifth and seventh days after birth. Jaundice associated with these changes is designated *physiologic* and is believed to be the result of increased bilirubin production from the breakdown of fetal RBCs combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6–7% of full-term infants have indirect bilirubin levels >13 mg/dL, and <3% have levels >15 mg/dL. Risk factors for elevated indirect bilirubin include maternal age, ethnicity (Chinese, Japanese, Korean, Native American), maternal diabetes, prematurity, drugs, altitude, polycythemia, male, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breastfeeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history of, or a sibling who had, physiologic jaundice (see Table 137.1). In infants without these variables, indirect bilirubin levels rarely rise >12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels. A combination of breastfeeding, variant-glucuronosyltransferase activity (1A1), subclinical glucose-6-phosphate dehydrogenase (G6PD) deficiency, and alterations of the organic anion transporter-2 gene increases the risk of hyperbilirubinemia. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on *hour-specific* bilirubin levels in the first 24-72 hours of life (Fig. 137.3). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 weeks suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be the result of caloric deprivation, relative deficiency of hepatic UDP–glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from an ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the fourth to seventh day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice based on the history, clinical findings, and laboratory data (see Table 137.3). In general, a search to determine the cause of jaundice should be made if (1) it appears in the first 24-36 hours after birth, (2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr, (3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant, (4) jaundice persists after 10-14 days after birth, or (5) direct bilirubin fraction is >2 mg/dL at any time. Other factors suggesting a pathologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, bleeding disorder, and signs of kernicterus (see Chapter 137.1).

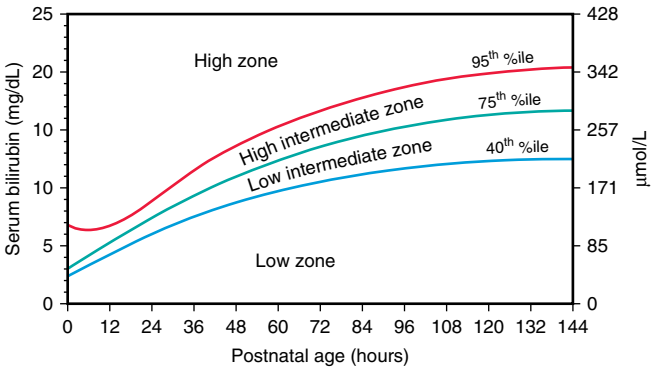

Fig. 137.3 Neonatal bilirubin nomogram. Percentile designation of well newborns ≥35 weeks' gestational age based on their hour-specific serum bilirubin values. The high zone is subdivided by the 95th percentile track. The intermediate zone is subdivided into upper and lower zones by the 75th percentile track. The low zone has been electively and statistically defined by the 40th percentile track. *(Modified from Bahr TM, Henry E, Christensen RD, et al. A new hour-specific serum bilirubin nomogram for neonates ≥35 weeks of gestation. J Pediatr. 2021;236:28–33. Fig. 2.)*

PATHOLOGIC HYPERBILIRUBINEMIA

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice, or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of unconjugated bilirubin, but many infants with this finding have associated risk factors such as ethnicity, prematurity, breastfeeding, and weight loss. Frequently, the terms *exaggerated physiologic jaundice* and *hyperbilirubinemia of the newborn* are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase **(Gilbert syndrome)** rather than an excessive load of bilirubin for excretion (see Table 137.1). *The combination of G6PD deficiency and a pathogenic variant of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis.*

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels (see Chapter 137.1). The development of kernicterus **(bilirubin encephalopathy)** depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, sepsis, meningitis, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. *The exact serum indirect bilirubin level that is harmful for very low birthweight (VLBW) infants is unclear.*

JAUNDICE ASSOCIATED WITH BREASTFEEDING

Significant elevation in unconjugated bilirubin **(breast milk jaundice)** develops in an estimated 2% of breastfed term infants after the seventh day, with maximal concentrations as high as 10-30 mg/dL reached during the second to third week. If breastfeeding is continued, the bilirubin gradually decreases but may persist for 3-10 weeks at lower levels. Phototherapy may be of benefit (see Chapter 137.1). Although very uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear, although intestinal β-glucuronidase resulting in deconjugation of bilirubin and increased enterohepatic circulation and other factors in breast milk that might interfere with bilirubin conjugation (e.g., pregnanediol, free fatty acids) have been implicated.

The late jaundice associated with breast milk should be distinguished from an *early onset*, accentuated unconjugated hyperbilirubinemia known as suboptimal intake hyperbilirubinemia or **breastfeeding jaundice**, which occurs during the first week after birth in breastfed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 137.4). Lower milk intake before breast milk production is established can result in various degrees of dehydration, which hemoconcentrates bilirubin, while also causing fewer bowel movements, which in turn increases the enterohepatic circulation of bilirubin. Prophylactic supplements of glucose water to breastfed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk and *are not indicated*. Frequent breastfeeding (>10 in 24 hours), rooming-in with night feeding, and ongoing lactation support may reduce the incidence of

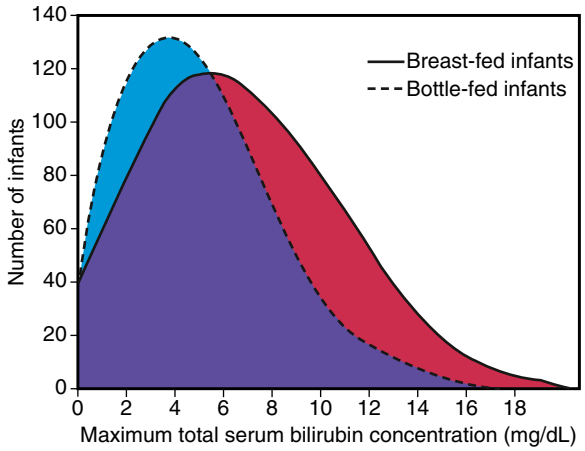

Fig. 137.4 Distribution of maximal bilirubin levels during the first week of life in breastfed and formula-fed White infants weighing >2,500 g. *(From Maisels MJ, Gifford K. Normal serum bilirubin levels in the newborn and the effect of breast-feeding. Pediatrics. 1986;78:837–843.)*

early breastfeeding jaundice. In addition, supplementation with formula or more preferred expressed breast milk is appropriate if the intake seems inadequate, weight loss is excessive, or the infant appears dehydrated.

NEONATAL CHOLESTASIS

See Chapter 404.

CONGENITAL ATRESIA OF THE BILE DUCTS

See Chapter 404.1.

Jaundice persisting for >2 weeks or associated with acholic stools and dark urine suggests biliary atresia. All infants with such findings require immediate diagnostic evaluation, including determination of direct bilirubin.

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137.1 Kernicterus and Therapy of Hyperbilirubinemia

Kelsey S. Ryan and Robert M. Kliegman

Kernicterus, or **bilirubin encephalopathy**, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the BBB, and neuronal susceptibility to injury. Disruption of the BBB by disease, asphyxia, infection, and other factors and maturational changes in BBB permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable. In a large series, however, kernicterus occurred only in infants with a bilirubin >20 mg/dL (more often >25-30 mg/dL), 90% of whom were previously healthy, predominantly breastfed, term and near-term infants. The duration of exposure to high bilirubin levels needed to produce toxic effects is unknown; the more immature the infant, and possibly age (day 1 vs day of life ≥4), the greater the susceptibility to kernicterus.

CLINICAL MANIFESTATIONS

Signs and symptoms of kernicterus usually appear 2-5 days after birth in term infants and as late as the seventh day in preterm infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, apnea, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill, high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 137.5). Rigidity is rare at this late stage.

Table 137.5 Clinical Features of Kernicterus

ACUTE FORM
Phase 1 (first 1-2 days): poor suck, stupor, hypotonia, seizures
Phase 2 (middle of first week): hypertonia of extensor muscles, opisthotonos, retrocollis, fever
Phase 3 (after the first week): hypertonia
CHRONIC FORM
First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills
After first year: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

From Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. *N Engl J Med* 2001;344:581–590.

Many infants who progress to these severe neurologic signs die; the survivors usually have serious sequalae but may appear to recover and for 2-3 months show few abnormalities. Later in the first year, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the second year the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 years of age, the complete neurologic syndrome is often apparent: bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or "minimal brain dysfunction," occurring singly or in combination; these problems may be unapparent until the child enters school (see Table 137.5).

INCIDENCE AND PROGNOSIS

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2–16% and is related to the risk factors discussed in this chapter. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs carry a grave prognosis; >75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Developmental delay, deafness, and spastic quadriplegia are common.

PREVENTION

The aim of bilirubin management is prevention of kernicterus. Although kernicterus has been thought to be a disease of the past, there are reports of neurotoxic effects of bilirubin in term and near-term infants who were discharged as healthy newborns. Effective prevention requires ongoing vigilance and a practical, system-based approach to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Predischarge universal screening for hyperbilirubinemia and assessment of clinical risk factors for severe jaundice and bilirubin-induced neurologic dysfunction include either total serum bilirubin or transcutaneous bilirubin measurement (interchangeably), although transcutaneous instruments may be less accurate at higher bilirubin levels (>15 mg/dL) or for infants with darker skin or if phototherapy has been used. If transcutaneous levels are documented as ≥15 mg/dL or rising rapidly, confirmation with a total serum bilirubin is recommended. Serum

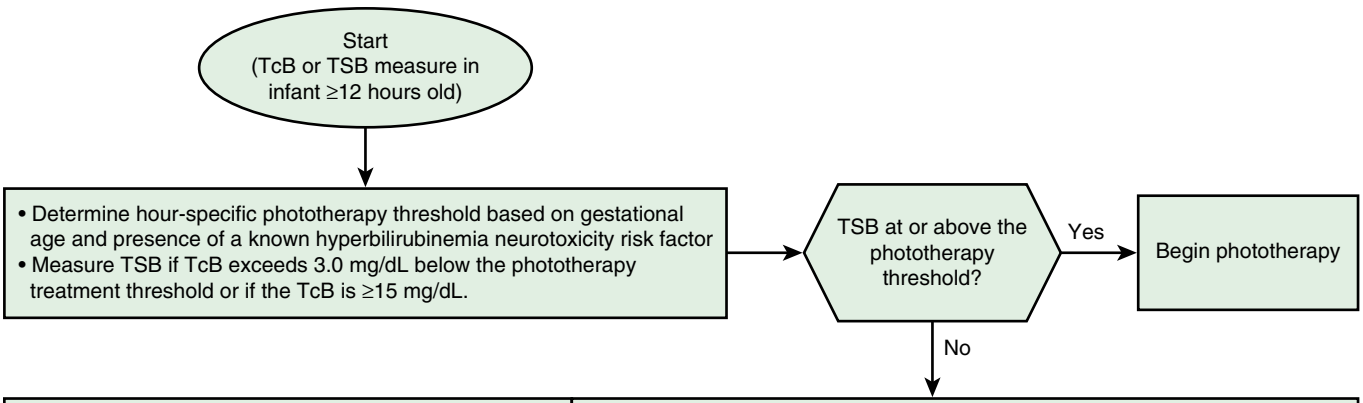
values should also be measured once infants begin phototherapy, because transcutaneous measurement may falsely underestimate total bilirubin in this setting.

Protocols using the hour-specific bilirubin nomogram (see Fig. 137.3), physical examination, and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. Potentially preventable causes of kernicterus include (1) early discharge (<48 hours) with no early follow-up (within 48 hours of discharge), a problem that is particularly important in near-term infants (35-37 weeks of gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the first 24 hours; (3) failure to recognize the presence of risk factors for hyperbilirubinemia, especially hemolysis; (4) underestimation of the severity of jaundice by clinical (visual) assessment, which is inaccurate; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. Figure 137.5 provides a consensus-based (expert opinion) management plan for neonates with significant hyperbilirubinemia that relies on consensus-recommended (expert opinion) phototherapy thresholds for gestational ages ≥35 weeks (Figs. 137.6 and 137.7) in well appearing neonates.

The following approach is further recommended: (1) any infant who is jaundiced before 24 hours requires measurement of total *and* direct serum bilirubin levels and, if elevated, evaluation for possible hemolytic or primary hepatic diseases, and (2) follow-up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48 hours after birth. Early follow-up is particularly important for infants <38 weeks of gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hours is necessary. Postdischarge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about the infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Parents should be advised to nurse their infants 8-12 times in 24 hours and to avoid supplementation with water or glucose water to ensure adequate hydration and caloric intake.

TREATMENT OF HYPERBILIRUBINEMIA

Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while causing no undue harm. Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Table 137.6; see Figs. 137.6 and 137.7). The risk of injury to the central nervous system from bilirubin must be balanced against the potential risk of treatment. Because phototherapy may require 6-12 hours to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion. When identified, underlying



Phototherapy threshold minus TcB or TSDB		Discharge recommendations
0.1-1.9 mg/dL	Age <24 hours	Delay discharge, consider phototherapy, measure TSB in 4 to 8 hours
	Age ≥24 hours	Measure TSB in 4 to 24 hours[a] Options: • Delay discharge and consider phototherapy • Discharge with home phototherapy if all considerations in the guideline are met • Discharge without phototherapy but with close follow-up
2.0-3.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 4 to 24 hours[a]
3.5-5.4 mg/dL	Regardless of age or discharge time	TSB or TcB in 1-2 days
5.5-6.9 mg/dL	Discharging <72 hours	Follow-up within 2 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]
≥7.0 mg/dL	Discharging <72 hours	Follow-up within 3 days; TcB or TSB according to clinical judgment[b]
	Discharging ≥72 hours	Clinical judgment[b]

Fig. 137.5 Algorithm to determine postdischarge follow-up for infants who have not received phototherapy during the birth hospitalization. [a]Use clinical judgment and shared decision-making to determine when to repeat the bilirubin measure within this 4–24-hour time window. [b]Clinical judgment decisions should include physical examination, the presence of risk factors for the development of hyperbilirubinemia or hyperbilirubinemia neurotoxicity risk factors, feeding adequacy, weight trajectory, and family support. TcB, Transcutaneous bilirubin; TSB, total serum bilirubin. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022; 150[3]:e2022058859. Fig. 7.)*

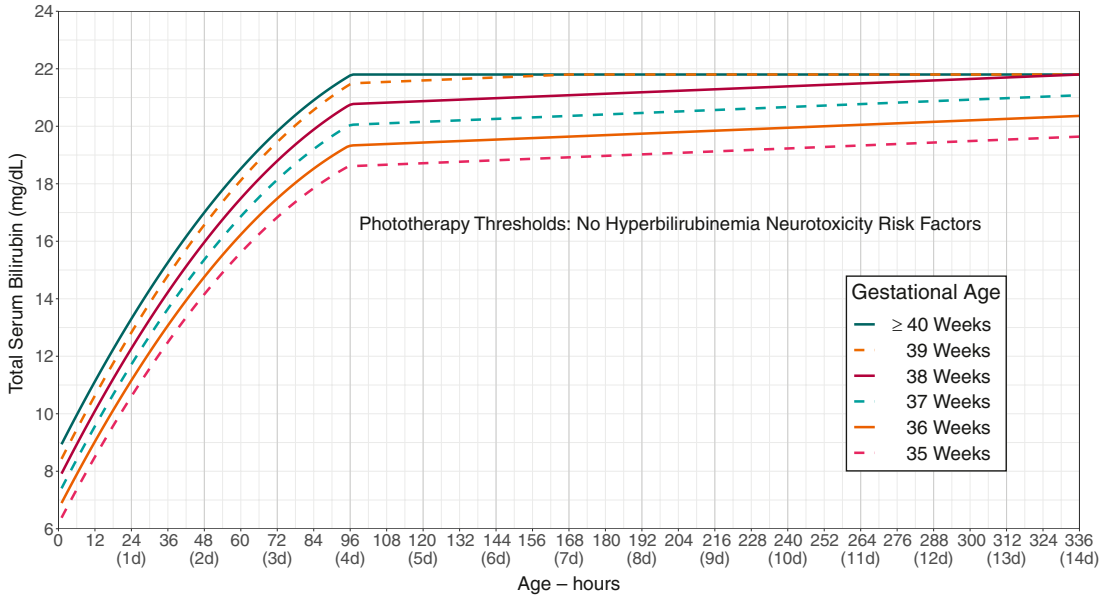


Fig. 137.6 Phototherapy thresholds by gestational age and age in hours for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Note that infants <24 hours old with a TSB at or above the phototherapy threshold are likely to have a hemolytic process and should be evaluated for hemolytic disease. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 2.)*

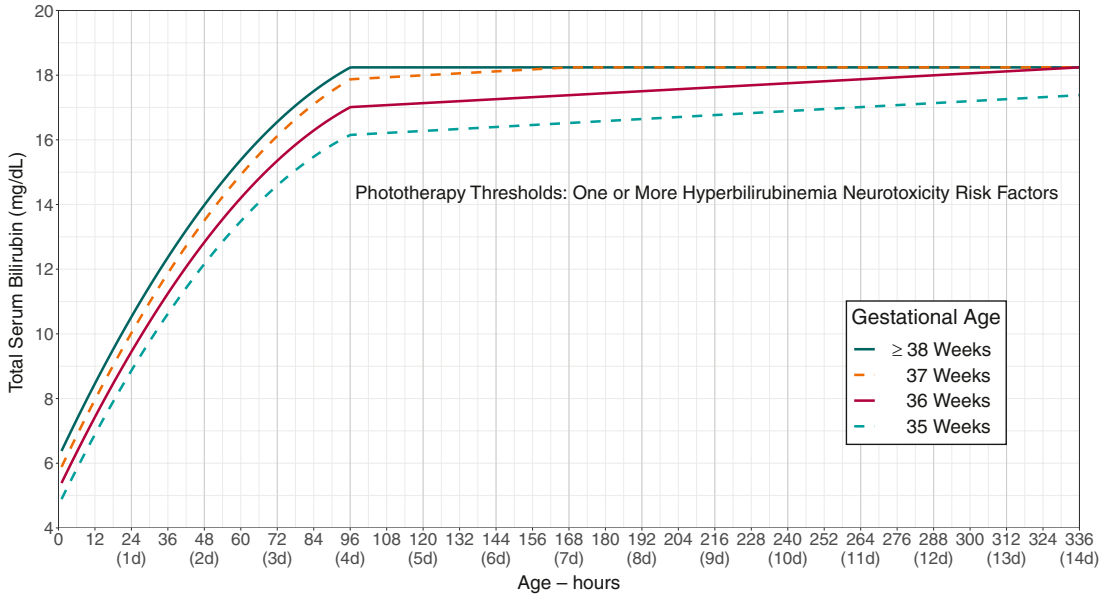


Fig. 137.7 Phototherapy thresholds by gestational age and age in hours for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin concentrations; do not subtract the direct-reacting or conjugated bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022:150[3]:e2022058859. Fig. 3.)*

medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated, such as antibiotics for sepsis, correction of acidosis, and dehydration (Fig. 137.8).

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to high-intensity light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photoisomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of hemolysis and in vivo metabolism and excretion of bilirubin. Available commercial phototherapy units vary considerably in spectral output and the intensity of radiance emitted; therefore the wattage can be accurately measured only at the patient's skin surface. Dark skin does not reduce the efficacy of phototherapy. Maximal intensive phototherapy should be used when indirect bilirubin levels approach those noted in Figures 137.6 and 137.7. Such therapy includes using LED lamps and/or putting a fiberoptic phototherapy blanket under the infant's back to increase the exposed surface area.

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic *and* nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis. Conventional phototherapy is applied continuously (except for breastfeeding). It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant's age and condition. Serum bilirubin levels and hematocrit should be monitored every 4-8 hours in infants with hemolytic disease and those with bilirubin levels near toxic range. Serum bilirubin monitoring should continue for at least 24 hours after cessation of phototherapy in *patients with hemolytic disease*, because unexpected rises in bilirubin may occur, requiring further treatment. Skin color, visual assessment, or transcutaneous bilirubin levels cannot be relied on for evaluating the effectiveness of phototherapy; the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia. Although not necessary for *all* affected infants, intravenous fluid supplementation added to oral feedings are beneficial in dehydrated patients or infants with bilirubin levels nearing those requiring exchange transfusion.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, hypothermia from exposure, and a benign condition called "bronze baby syndrome," which occurs in the presence of direct hyperbilirubinemia. Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage and fluorescent bulb use. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development

Table 137.6 Suggested Maximal Indirect Serum Bilirubin Concentrations (mg/dL) in Preterm Infants

BIRTHWEIGHT (g)	UNCOMPLICATED*	COMPLICATED*
<1,000	12-13	10-12
1,000-1,250	12-14	10-12
1,251-1,499	14-16	12-14
1,500-1,999	16-20	15-17
2,000-2,500	20-22	18-20

*Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50–70% of the maximal indirect level. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.

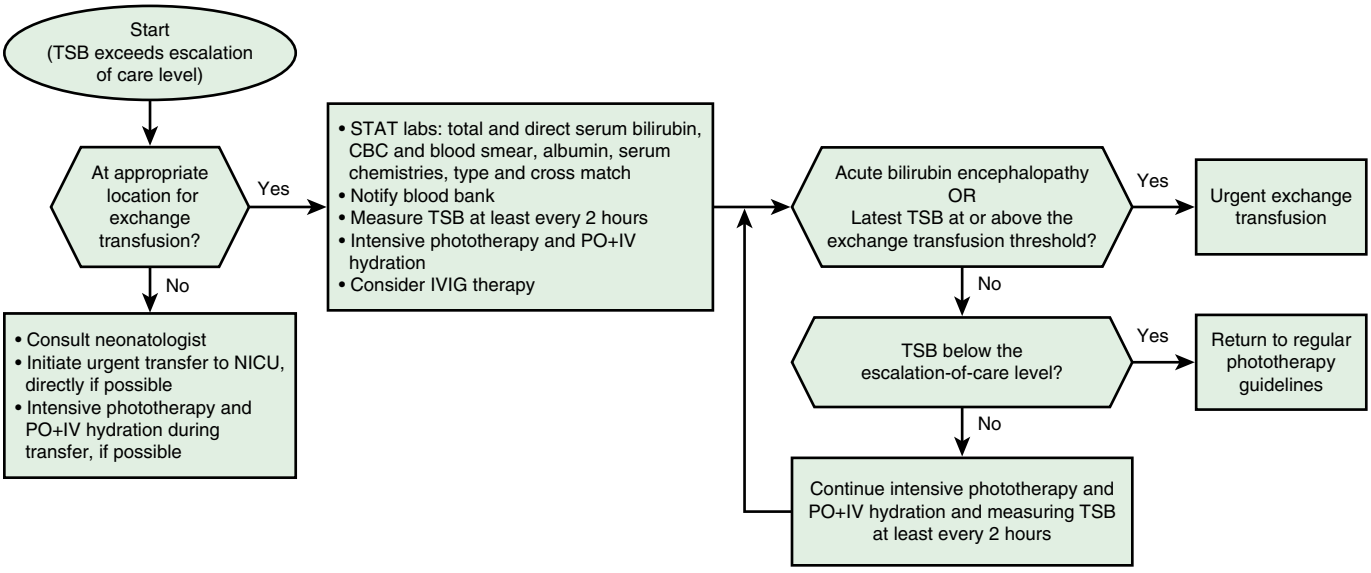


Fig. 137.8 Approach to escalation of care. The escalation-of-care threshold is 2 mg/dL below the exchange transfusion threshold. IVIG, Intravenous immunoglobulin; NICU, neonatal intensive care unit; PO, orally; TSB, total serum bilirubin. *(Modified from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 4.)*

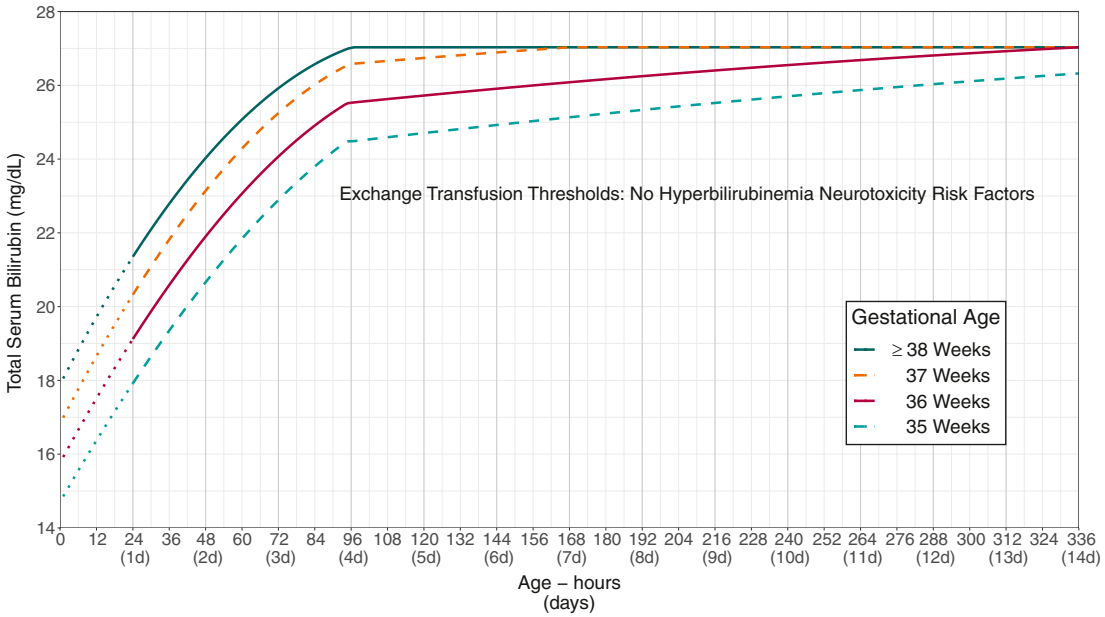


Fig. 137.9 Exchange transfusion thresholds by gestational age for infants with no recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 5.)*

of anemia, which may require transfusion; *anemia may develop despite lowering of bilirubin levels.* Clinical experience suggests that long-term adverse biologic effects of phototherapy are absent, minimal, or unrecognized.

The term **bronze baby syndrome** refers to a dark, grayish brown skin discoloration sometimes noted in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may result from photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin

The administration of intravenous immunoglobulin (IVIG) is an adjunctive treatment for hyperbilirubinemia caused by *isoimmune hemolytic disease*. It has been used when serum bilirubin is approaching exchange levels despite maximal interventions, including phototherapy. IVIG (0.5-1.0 g/kg/dose; repeat in 12 hours) may reduce the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis. The effectiveness is unclear.

Exchange Transfusion

Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and the risk of kernicterus exceeds the procedural risk. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, necrotizing enterocolitis (NEC), infection, graft versus host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (Fig. 137.9). Ideally the exchange transfusion should be performed with leukocyte-depleted, washed fresh-packed RBC's, reconstructed with fresh-frozen plasma to a hematocrit of ~40%. It should be cross matched against the neonate and the mother.

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient (see Fig. 137.8). The appearance of clinical signs suggesting kernicterus is an absolute indication for exchange transfusion at any level of serum bilirubin. A hydropic jaundiced neonate with erythroblastosis from Rh disease will be critically ill and requires exchange transfusion at much lower levels than recommended in Figures 137.9 and 137.10. See other risk factors affecting exchange transfusion threshold in Figure 137.10.

A healthy full-term infant with physiologic or breast milk jaundice may tolerate a bilirubin concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level. A level approaching that considered critical for the individual infant may be an indication for exchange transfusion during the first or second day after birth, when a further rise is anticipated, but not typically after the fourth day in a term infant or after the seventh day in a preterm infant, because an imminent decrease in bilirubin levels may be anticipated as the hepatic conjugating mechanism becomes more effective.

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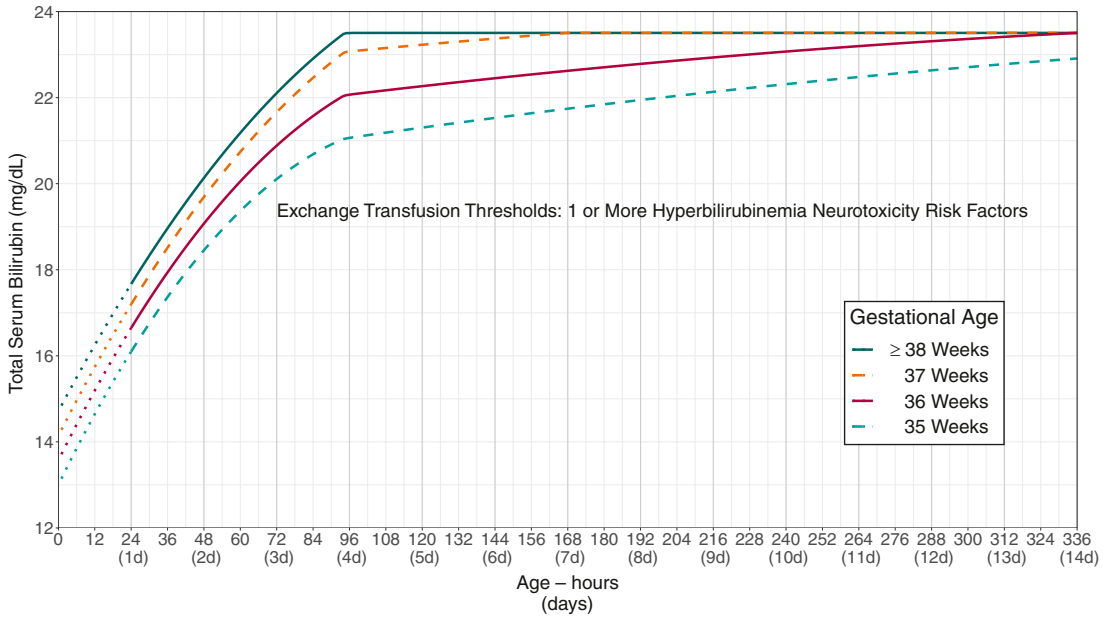

Fig. 137.10 Exchange transfusion thresholds by gestational age for infants with any recognized hyperbilirubinemia neurotoxicity risk factors other than gestational age. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The stippled lines for the first 24 hours indicate uncertainty because of the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin concentrations; do not subtract direct bilirubin from the total serum bilirubin. In rare cases of severe hyperbilirubinemia in which the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or other hemolytic conditions; sepsis; or any significant clinical instability in the previous 24 hours. *(From Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2022;150[3]:e2022058859. Fig. 6.)*

Chapter 138

Blood Disorders

Christopher S. Thom and Michele P. Lambert

NORMAL ERYTHROPOIESIS AND HEMOGLOBIN FUNCTIONS

The diagnosis of anemia or polycythemia, and interpretation of laboratory values, requires understanding normal hemoglobin-oxygen binding and delivery physiology. Heterotetrameric **hemoglobin**, comprising two α-globin and two β-globin monomers, has an exquisite ability to cooperatively bind and release oxygen molecules in response to environmental conditions. Hemoglobin switching refers to the normal transitions in gene expression among embryonic, fetal, and adult globins that occur before and after birth (Fig. 138.1). Fetal hemoglobin (HbF) is the predominant hemoglobin molecule produced during late gestation. Its increased oxygen affinity compared with maternal adult hemoglobin (HbA) facilitates oxygen transfer in the hypoxic in utero environment, which lacks direct atmospheric gas exchange. Relative in utero hypoxia explains the elevated hemoglobin levels normally seen in newborns, which can be exacerbated by pathologic chronic intrauterine hypoxia.

NORMAL RED BLOOD CELL INDICES IN NEONATES AND INFANTS

Diagnosing anemia or polycythemia in infants also relies on comparisons to normal reference ranges, which vary based on gestational and postnatal age. Normal reference ranges for hemoglobin, hematocrit, and other erythrocyte indices are based on measurements from more than 25,000 preterm and term infants through the first 28 days of life (Fig. 138.2). Hemoglobin and hematocrit levels exhibit linear increases between 22 and 40 weeks of gestation.

Erythrocyte mean corpuscular volume (MCV) in neonates is typically higher than toddlers or older children, with normal values ranging from approximately 100-115 fL at birth (see Fig. 138.2C). Reasons for this finding are multifactorial. An elevated MCV can reflect an increase in circulating reticulocytes (immature erythrocytes), although a relative reticulocytosis in neonates is inadequate to fully explain the MCV elevation. Indeed, mature erythrocytes are larger in neonates than in adults. The size discrepancy may be related to the presence of different hemoglobin molecules, as mature erythrocytes containing HbF (termed F cells) may be larger than HbA-containing cells. Conversely, MCV <100 fL in a neonate should prompt suspicion for underlying α-thalassemia/thalassemia trait, maternal iron deficiency, or chronic fetal to maternal blood loss.

At any age, increased MCV can indicate hemolysis or other processes that enhance erythropoietic drive. Persistent microcytic anemia can result from thalassemia or iron deficiency.

Platelet Count Abnormalities in Pediatric Patients

Hematopoiesis, megakaryopoiesis, and thrombopoiesis produce ~10^{11} platelets per day to facilitate normal blood clotting and fulfill important vascular functions (see Chapter 495). Processes that disrupt platelet production or consumption can significantly alter steady-state platelet quantities in circulation. This can be clinically relevant and require intervention, although many etiologies are transient and/or benign. Here we describe common etiologies that increase or decrease platelet counts. Chapter 533 includes a full description of these and other platelet defects.

Thrombocytosis is defined as >450 × 10^9 platelets/L blood, although for neonates this limit can be raised to >600 × 10^9 platelets/L. Thrombocytosis can be stratified from mild to extreme, the latter defined as >1,000 × 10^9

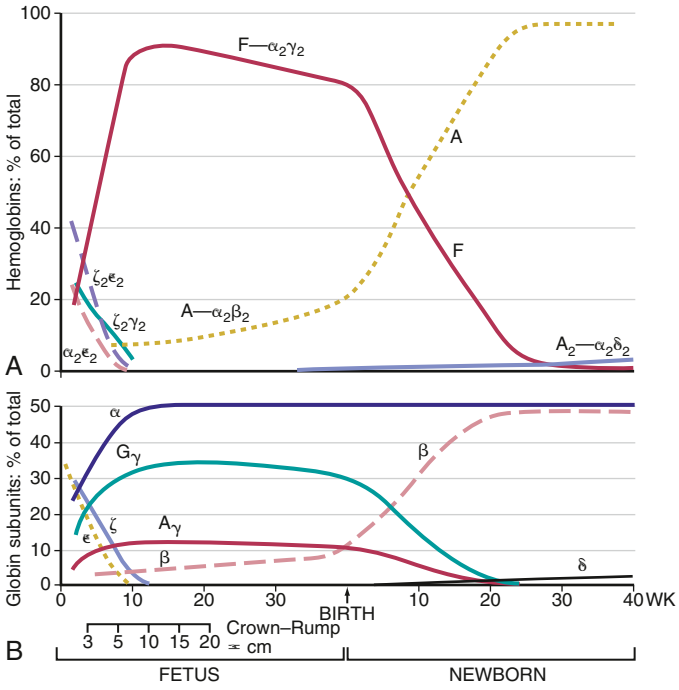

Fig. 138.1 Developmental changes in (A) hemoglobin tetramers and (B) globin subunit expression from early gestation through infancy. (*From Polin RA, Fox WW. Fetal and Neonatal Physiology. 2nd ed. Philadelphia: Saunders; 1998. p. 1769.*)

platelets/L. Immature immune or hematopoietic systems may underlie an increased rate of thrombocytosis in infants and young children.

Myeloproliferative disorders can cause primary thrombocytosis, but this is rare in children. More often, thrombocytosis reflects a secondary or reactive process as part of an acute phase response. This is usually due to an inflammatory process and does not increase thrombotic risk in children. Extreme thrombocytosis is rare, and it can be more worrisome for infection, iron deficiency, or other inflammatory pathology. However, even extremely elevated platelet counts do not seem to increase risk of hemorrhage or thrombosis. Thus most often, thrombocytosis will resolve spontaneously, or after treatment of the inciting etiology, without adverse sequelae.

Thrombocytopenia is defined as platelets count <150 × 10^9 platelets/L blood. However, increased bleeding risk does not typically occur unless platelet counts decline to <20 × 10^9 platelets/L. Congenital and acquired processes underlie a broad differential diagnosis for thrombocytopenia that is described in Chapter 533. Different immune and nonimmune processes can cause thrombocytopenia at different stages of infancy or later childhood, with wide-ranging health implications.

NEUTROPENIA

White blood cells provide innate and adaptive immune functions. The neutrophil is a key component of innate immune surveillance, and disorders that affect neutrophil number and function can result in varied clinical consequences (see Chapter 168).

Neutropenia is defined as an absolute neutrophil count (ANC) <1,500/μL blood, but typically increases infection risk only when ANC falls <500/μL. Many processes affecting the survival of neutrophils and their precursor cells can cause neutropenia, including situations wherein antineutrophil antibodies increase neutrophil destruction and clearance.

Autoimmune neutropenia results from a patient's own neutrophil-targeted antibodies. It is among the most common etiologies of neutropenia in infants and toddlers, rarely results in significant infections or complications, and generally resolves by the time the child is school age. Neonatal isoimmune neutropenia results from transplacental passage of maternal antineutrophil antibodies in a process akin to red blood cell (RBC) antigen-targeted antibodies in hemolytic disease of the fetus and newborn (see Chapter 140). Importantly, these scenarios do not typically incur additional infection risks for patients. In fact, they are typically diagnosed incidentally after noting abnormalities on a complete blood count obtained for other reasons. Reassurance, with or without repeat laboratory testing, is typically all that is required. Counts will virtually always normalize spontaneously.

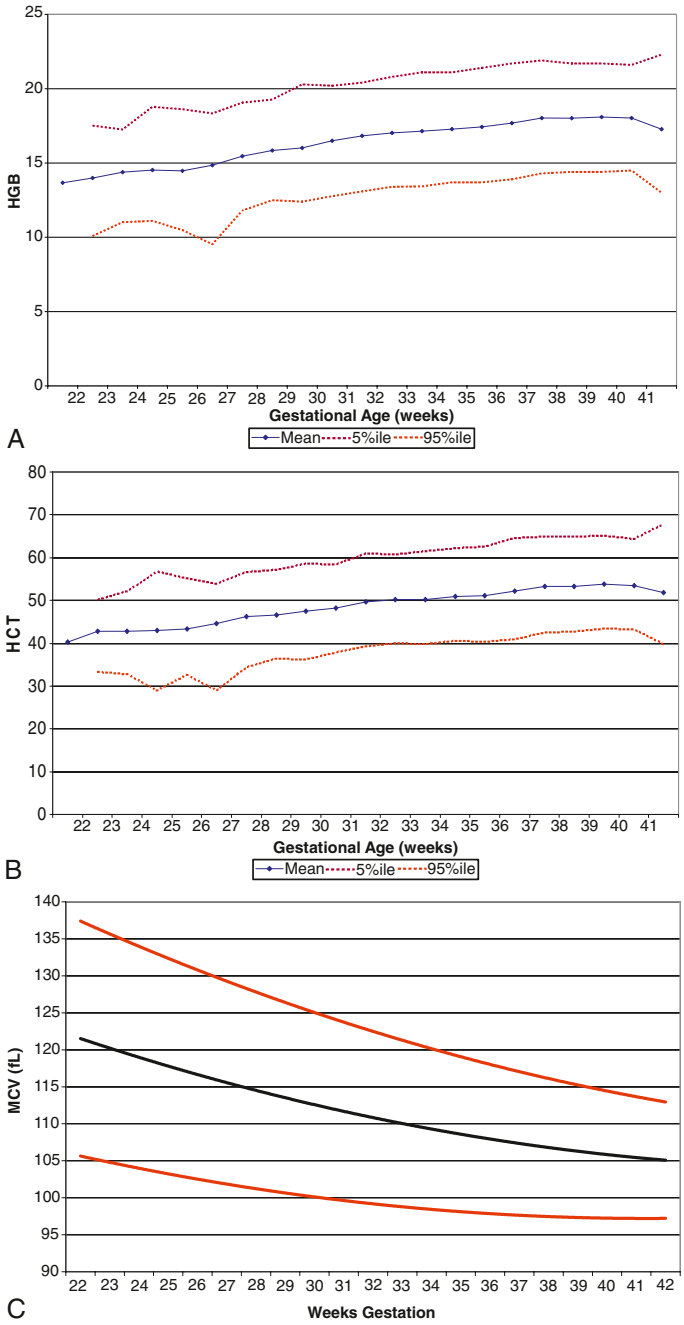

Fig. 138.2 Reference range for hematocrit (HCT) and hemoglobin (HGB) concentration according to gestational age. A and B, Reference ranges (5th percentile, mean, and 95th percentile) are shown for blood HGB (A) and HCT (B). Concentrations were obtained during the first 6 hours after birth, among patients at 22-42 weeks of gestation. Values were excluded if the diagnosis included abruption, placenta previa, or known fetal anemia, or if a blood transfusion was given before the first HGB was measured. C, Reference ranges for mean corpuscular volume (MCV) in neonates on first day after birth. The *lower line* shows the 5th percentile values, the *middle line* shows the mean values, and the *upper line* shows the 95th percentile values. (*From Christensen RD, Jopling HE, Jopling J, Wiedmeier SE. The CBC: Reference ranges for neonates. Semin Perinatol. 2009;33[1]:3–11.*)

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Chapter 139

Anemia in the Newborn Infant

Christopher S. Thom and Michele P. Lambert

Anemia is extremely common worldwide, affecting an estimated 25% of the global population, and carries a broad differential diagnosis in infants and children. Etiologies may be acute or chronic, with clinical manifestations ranging from an asymptomatic laboratory finding to life-threatening signs and symptoms. Because anemia can result from decreased erythrocyte production, increased erythrocyte destruction, erythrocyte dysfunction, or blood loss, the differential diagnosis of anemia can be complex (Table 139.1). Careful consideration of details related to the patient's history and presentation can facilitate rapid diagnosis. Additional relevant details in neonates include gestational age and general health, perinatal course and delivery, and maternal health from early pregnancy through delivery and the postpartum period.

THE PHYSIOLOGIC NADIR DURING INFANCY

An abrupt increase in oxygen tension and arterial hemoglobin saturation, a shift in the oxygen dissociation curve due to a switch from high oxygen affinity fetal hemoglobin (HbF) to low oxygen affinity adult hemoglobin (HbA), increased postnatal 2,3-diphosphoglycerate (increasing oxygen delivery through cooperativity), and adaptive cardiovascular mechanisms all contribute to increased oxygen delivery to tissues and can rapidly reduce erythropoietin levels postnatally. These mechanisms result in reduced erythropoiesis in the bone marrow after a week of life. Combined with the shorter half-life of neonatal erythrocytes compared to adult erythrocytes (60 days vs 120 days), full-term infants normally experience a slow decline in hemoglobin to 9-11 g/dL over 6-10 weeks (Fig. 139.1). Eventually, the reduction in hemoglobin concentration reduces oxygen delivery enough to stimulate erythropoietic drive, and hemoglobin levels subsequently rebound to "normal" levels for later life (see Fig. 139.1). These typical developmental and physiologic processes culminating in a decreased hemoglobin level are termed the **physiologic nadir**.

Preterm infants experience a more pronounced, earlier nadir, with hemoglobin levels falling to 8-9 g/dL over 4-8 weeks. One reason for the more dramatic nadir in preterm infants is reduced iron stores, because most iron is normally transferred to the fetus during the third trimester. The nadir in preterm infants is also a consequence of a reduced starting hemoglobin at birth; iatrogenic blood loss; and more significant cardiorespiratory disease, inadequate nutrition, and infections. Still, a hemoglobin level <8 typically prompts a transfusion and/or hematologist consultation.

Normal physiologic changes in hemoglobin concentration should be considered when diagnosing anemia in neonates and early infants. For example, a neonate may be considered anemic if the hemoglobin level declines below the 5th percentile for age (see Fig. 139.1, lower dashed lines). *Interventions should occur only in response to clinical signs and symptoms that occur as disease sequelae with referral to subspecialty care for further evaluation and management as appropriate.*

ANEMIA CLASSIFICATIONS AND KEY DIAGNOSTIC MODALITIES

Anemia can result from blood loss, erythrocyte destruction (hemolysis), or underproduction of erythrocytes. Common etiologies are summarized in Table 139.1. In many cases, the clinical context, physical examination, and medical history, including review of the patient's history and clinical course, can be diagnostic. However, a simple and efficient laboratory workup can facilitate rapid definitive diagnosis and suggest an effective treatment strategy (Fig. 139.2).

In many cases, a CBC and the reticulocyte count can identify the diagnosis. Additional testing that is particularly helpful in neonatal diagnosis includes a direct antiglobulin test, serum bilirubin, infant blood type, and maternal blood type (ABO and Rh). Prenatal screening routinely includes indirect (serum) antiglobulin testing for maternal erythrocyte alloantibodies. The infant's peripheral blood smear can identify nucleated erythrocytes secondary to compensatory active erythropoiesis, as well as distinct erythrocyte morphologies (e.g., elliptocytes, acanthocytes) reflecting hemolytic anemia. Spherocytes and microspherocytes can suggest immune-mediated hemolysis or hereditary spherocytosis (HS), which can be differentiated by the direct antiglobulin test (DAT; formerly the direct Coombs test; Fig. 139.3). Importantly, neonatal blood smears often include atypical erythrocyte morphology with macrocytosis, poikilocytosis, and anisocytosis, which can result from normal erythropoiesis at that age and preclude definitive diagnosis. An experienced hematology-pathologist is needed to identify truly pathologic features (Table 139.2; see Chapter 496).

Specialized testing to diagnose various red cell membrane disorders and enzyme deficiencies, as well as hemoglobin quantitation for evaluation for specific hemoglobin disorders, may be performed in consultation with a specialist. Some states routinely screen newborns for glucose-6-phosphate-dehydrogenase (G6PD) deficiency. Further, universal screening in the United States for sickle cell disease has markedly improved health outcomes by facilitating early penicillin prophylaxis, although much work remains to be done.

Inadequate Red Blood Cell Production

Whereas normal RBC underproduction after birth results in the **physiologic nadir**, this process can be more significant in preterm infants, requiring transfusions and other supportive therapy. **Anemia of prematurity** is largely due to iatrogenic losses (phlebotomy) and is exacerbated by acute or chronic illness, comorbidities of prematurity, and decreased iron stores.

Iron-deficiency anemia is the most common cause of anemia worldwide, and can occur during infancy or in older children. Iron is required

Table 139.1 Differential Diagnosis of Neonatal Anemia

BLOOD LOSS	↑ RBC DESTRUCTION	↓ RBC PRODUCTION
• Iatrogenic blood loss (phlebotomy) • Placental hemorrhage • Placental previa • Injury of umbilical or placental vessels • Fetomaternal transfusion • Fetoplacental transfusion • Twin-twin transfusion • Acute perinatal hemorrhage (e.g., cesarean birth, other obstetric trauma) • Chronic in utero blood loss	*Immune-Mediated Hemolysis* • Rh incompatibility • ABO incompatibility • Minor antigen incompatibility *RBC Membrane Disorders* • Hereditary spherocytosis • Hereditary elliptocytosis • Hereditary pyropoikilocytosis • Hereditary stomatocytosis *RBC Enzyme Disorders* • G6PD deficiency • Pyruvate kinase deficiency	• Physiologic anemia and anemia of prematurity • Infection (rubella, CMV, parvovirus B19) • Bone marrow suppression (acute stress in perinatal period) • Hemoglobinopathy (γ-globin mutation, unstable β-hemoglobinopathy, α-thalassemia major) • Bone marrow suppression (CMV, EBV) • Diamond-Blackfan anemia • Schwachman-Diamond syndrome • Congenital dyserythropoietic anemia • Fanconi anemia • Pearson syndrome • Congenital leukemia

CMV, Cytomegalovirus, EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase.

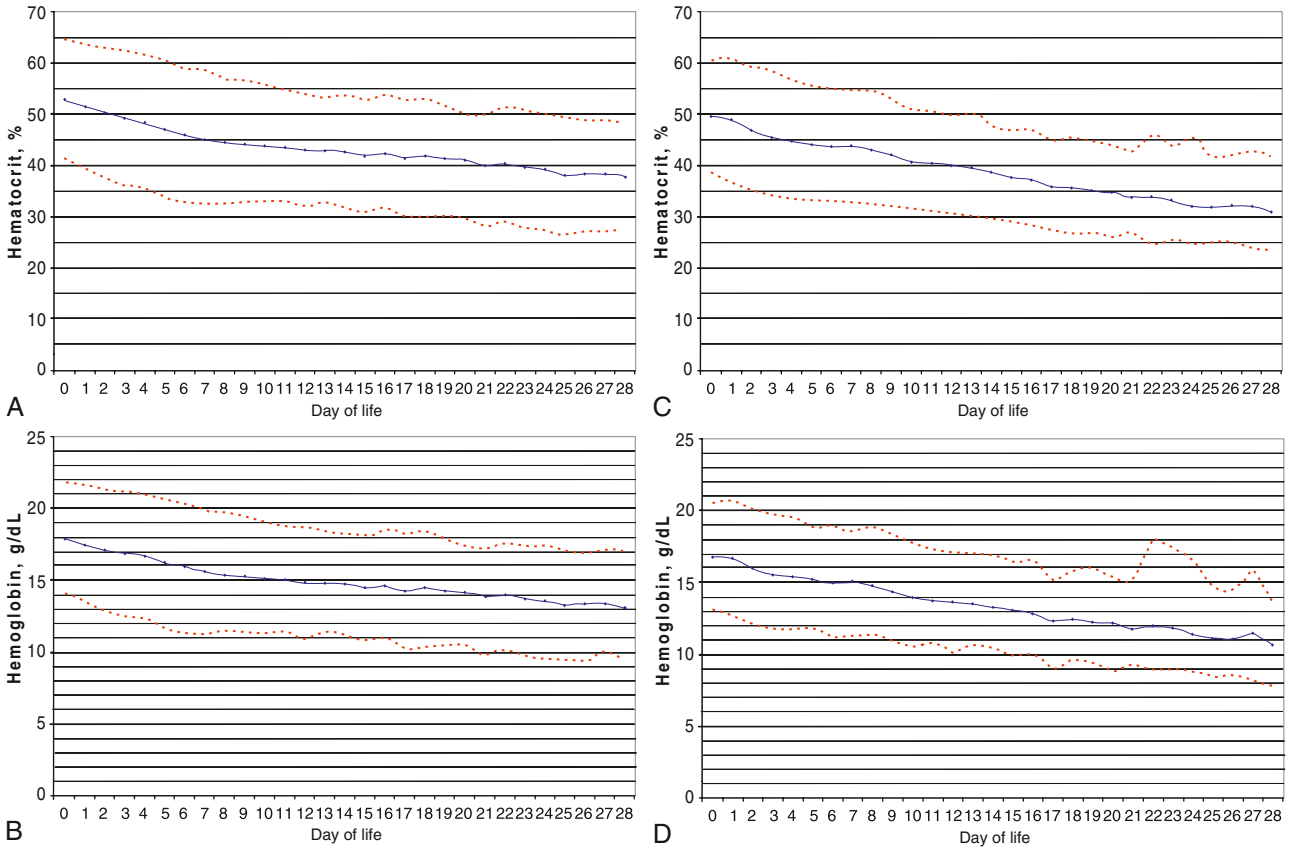

Fig. 139.1 Reference range for hematocrit and hemoglobin concentration during the first 28 days of life. **A** and **B**, Late preterm and term infants (35-42 weeks' gestation). **C** and **D**, Preterm infants (29-34 weeks' gestation). The reference ranges are shown for hematocrit (**A** and **C**) (41,957 patients) and blood hemoglobin (**B** and **D**) (39,559 patients) during the 28 days after birth. Values were divided into two groups (A/B and C/D) on the basis of gestational age at delivery. Patients were excluded when their diagnosis included abruption, placenta previa, or fetal anemia, or when a blood transfusion was given. Analysis was not possible for patients <29 weeks' gestation because virtually all these had repeated phlebotomy and erythrocyte transfusions. (*From Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. Pediatrics. 2009;123[2]:e333–e337.*)

for hemoglobin tetramer construction, so erythropoiesis demands ample iron be present to form hemoglobinized RBCs. Insufficient iron stores, either through chronic blood loss or inadequate iron intake, hinder erythropoiesis. RBCs will be uniformly microcytic (mean corpuscular volume [MCV] <80 fL) and hypochromic on the blood smear. Ferritin, transferrin, and reticulocyte quantities will be low. In addition to anemia, iron deficiency predisposes to thrombocytosis. This is a result of effects on hematopoietic progenitor cell lineage commitment, among potential mechanisms. Iron supplementation at doses of 3-6 mg/kg/day can effectively treat this condition; once-daily treatment is better than divided doses due to potential induction of hepcidin with frequent iron supplementation.

Acquired conditions may also suppress bone marrow erythrocyte production in neonates and older children (Table 139.3). Numerous bacterial and viral infections may suppress erythropoiesis and contribute to anemia, from prenatal TORCH (toxoplasmosis, other viral agents, rubella, cytomegalovirus [CMV], herpes simplex) infections and parvovirus B19 to sepsis. Congenital conditions may result in anemia due to decreased red cell production. These rare disorders may manifest early in the neonatal period, but more commonly present in later infancy or early childhood. Etiologies include the bone marrow failure syndromes (Fanconi anemia, Schwachman-Diamond syndrome, Diamond-Blackfan anemia, Aase syndrome congenital dyserythropoietic anemia, dyskeratosis congenita, Pearson syndrome), the thalassemias (α, β, or HbE), and infant leukemias, among others (see Tables 139.1 and 139.3).

Increased Red Cell Destruction: The Hemolytic Anemias

Increased rates of RBC destruction cause hemolytic anemia. This most often occurs via immune-mediated mechanisms, when RBC antigen incompatibilities exist between infants and mothers, or as a result of autoimmune disease in later childhood. However, intrinsic abnormalities in the erythrocyte membrane, hemoglobin, or other enzymes can also increase hemolysis. Severe hemolytic anemias can cause hyperbilirubinemia necessitating intervention (Fig. 139.4). For example**, hemolytic disease of the fetus and newborn (HDFN),** also known as erythroblastosis fetalis, results in often severe alloimmune hemolysis from maternal antibodies targeting paternally derived RBC antigens (see Chapter 140).

Congenital erythrocyte membrane disorders can cause clinically significant hemolytic anemia and jaundice in the neonatal period and beyond. Key structural proteins and lipid components are necessary to produce durable, flexible, biconcave erythrocyte membranes capable of deforming and squeezing through tiny capillaries. Genetic abnormalities in integral membrane proteins (e.g., ankyrin, band 3, α-spectrin, β-spectrin, protein 4.2) destabilize the RBC membrane and decrease cellular deformability, increasing splenic entrapment. HS is the most common RBC membrane disorder, affecting 1 in 2,500-5,000 individuals of European descent. HS is most often caused by pathogenic variants in genes coding for ankyrin or spectrin and is characterized by spherical erythrocytes on the blood smear (see Fig. 139.3; see Chapter 507). Most infants born with HS will develop jaundice early in the newborn period. *Treatment is largely supportive. Most patients with mild disease require little intervention, whereas those with more severe hemolysis sometimes require RBC transfusions or splenectomy.* Hereditary elliptocytosis (HE), another erythrocyte membranopathy, is typically less severe than HS. HE is characterized by elliptical-shaped erythrocytes on the peripheral blood smear and may be underdiagnosed given the extremely mild clinical presentation.

A more clinically significant membranopathy is hereditary pyropoikilocytosis (HPP), an autosomal recessive disorder with striking dysmorphology (poikilocytosis) on the peripheral blood smear. HPP is most common

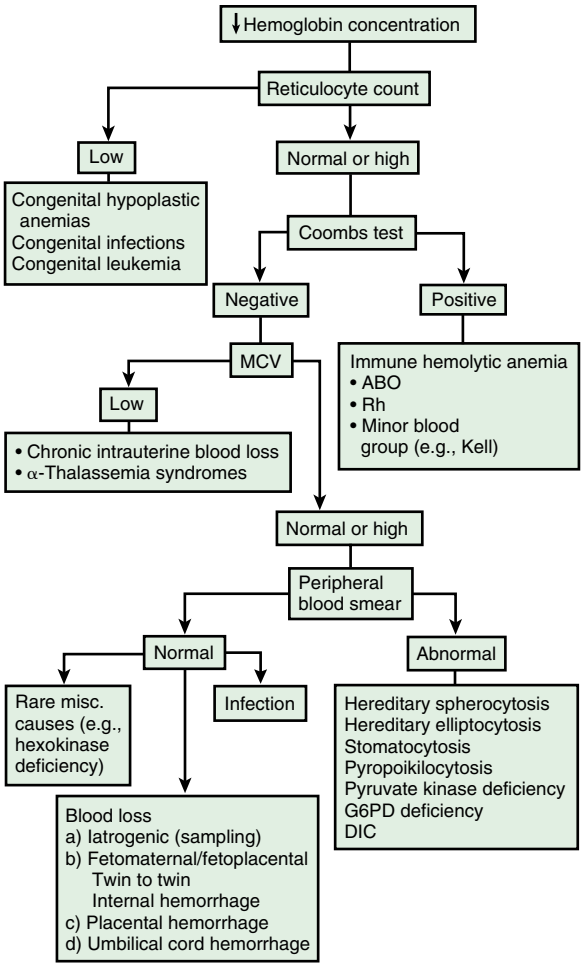

Fig. 139.2 Diagnostic algorithm showing the approach to anemia in newborn infants. DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; MCV, mean corpuscular volume. (*Modified from Blanchette VS, Zipursky A. Assessment of anemia in newborn infants. Clin Perinatol. 1984;11:489–510.*)

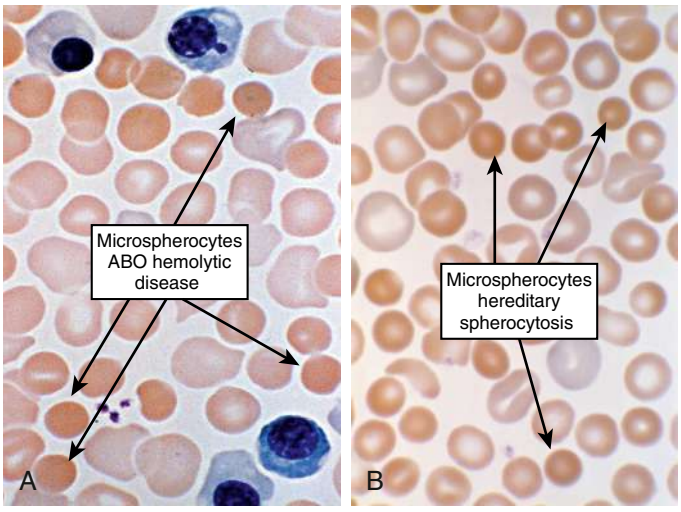

Fig. 139.3 Microspherocytes. **A,** Neonate with ABO hemolytic disease. **B,** Neonate with hereditary spherocytosis. (*From Christensen RD. Neonatal erythrocyte disorders. In Gleason CA, Juul SE, eds. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018: Fig. 81-8.*)

in infants of African descent and can be associated with severe anemia and hemolysis during infancy and throughout life. There is substantial clinical and genetic overlap between HPP and HE, because infants with HPP often have a family history of HE and may develop a milder condition resembling HE later in childhood (see Chapter 508).

In infants with significant jaundice in the first day of life without a blood type mismatch, a family history of hemolytic anemia should prompt clinical suspicion for an erythrocyte membranopathy. Beyond a negative DAT, diagnostic evaluation should include serial bilirubin and reticulocyte monitoring, along with a peripheral blood smear. Previously, osmotic fragility testing was the only way to establish the diagnosis, but it is significantly impacted by hemoglobin F concentrations. Some laboratories can instead diagnose certain membranopathies by flow cytometry based on binding of eosin-5-maleimide (EMA). Treatment is directed by the degree of anemia and hyperbilirubinemia, which can be highly variable.

Erythrocyte enzymopathies can also cause neonatal anemia. Circulating RBC survival relies on critical metabolic pathways to limit oxidative stress. Inadequate antioxidant systems can result in membrane instability and cell lysis that manifest clinically as hemolytic anemia. For example, G6PD is abundant in RBCs to limit oxidative stress. G6PD deficiency, the most common RBC enzymopathy, is an X-linked disorder affecting >400 million people worldwide. Different classes of G6PD deficiency vary in clinical severity. Although affected individuals are generally asymptomatic, some are prone to develop acute hemolytic anemia in the setting of oxidative stress triggered by sulfa drugs, infections, or certain foods like fava beans. There is an increased incidence of clinically significant jaundice in G6PD deficient neonates, who sometimes have severe and prolonged hyperbilirubinemia that can present in the first few days of life. Although severe anemia with reticulocytosis is uncommon, many infants require increased monitoring or therapy. Newborn screening for G6PD deficiency varies across the United States. G6PD activity can be tested in erythrocytes (<1–2% suggests G6PD deficiency). However, testing may be inaccurate during acute hemolysis or reticulocytosis because, for the most common variants, reticulocytes have higher enzyme activity.

Another common RBC enzymopathy is pyruvate kinase deficiency (PKD), which affects an estimated 3.2-8.5 per million individuals of European descent. Pyruvate kinase is a critical glycolytic enzyme. In its absence, metabolic derangements can cause RBC lysis and hemolytic anemia. Though clinical severity varies, PKD may be associated with sometimes life-threatening complications, prolonged jaundice, and lifelong blood transfusions.

HEMOGLOBINOPATHIES

Hemoglobinopathies result from genetic variants in γ-globin, β-globin, or α-globin genes. The clinical presentation of hemoglobin variants reflects aberrant biochemical properties of the mutated hemoglobin molecule. Individuals can be anemic (most commonly), cyanotic, polycythemic, prone to hemolysis, have high methemoglobin levels, or asymptomatic. Thousands of variants have been identified, with wide-ranging clinical severity.

Hemoglobin variants can also clinically manifest at different times according to when the affected globin chain is produced (see Fig. 138.1). The common β-hemoglobinopathies, sickle cell disease and β-thalassemia, do not typically present in the neonatal period due to protective effects from high HbF levels. In fact, novel therapeutic approaches aim to maintain HbF persistence in sickle cell patients. In contrast, infants with rare γ-globin variants can present with complications in the neonatal period that resolve in the first few months of life as normal gene expression changes to reduce or abrogate γ-globin expression.

Hemorrhage and Red Blood Cell Loss

Blood loss or hemorrhage in utero or in the newborn period can also result in anemia. In fact, iatrogenic or pathologic blood loss is the most common cause of neonatal anemia. For critically ill and/or premature infants in the neonatal intensive care unit (NICU), laboratory monitoring can require phlebotomy of 15–30% of an infant's blood volume every week (~11-22 mL/kg/week). Most other blood loss etiologies occur just before or during delivery, often from placental abruption or fetal hemorrhage (see Table 139.1). Infants can also become anemic from occult gastrointestinal blood losses due to milk protein allergy. Other causes of blood loss are restricted

Table 139.2 Morphologic Abnormalities of Erythrocytes in Neonates with Jaundice

ABNORMAL ERYTHROCYTE MORPHOLOGY	MOST LIKELY CAUSES	SUGGESTED LABORATORY TESTING/FINDINGS	OTHER FEATURES
Microspherocytes	Hereditary spherocytosis	DAT (–) EMA flow (+) Persistent spherocytosis Reticulocytosis	MCHC/MCV elevated (>36, likely >40)
	ABO hemolytic disease	DAT (+) Transient spherocytosis Reticulocytosis	MCHC/MCV normal (<36, likely <34)
Elliptocytes	Hereditary elliptocytosis	DAT (–)	MCHC normal MCV normal
Bite and blister cells	G6PD deficiency Unstable hemoglobin	G6PD enzyme activity Heinz body preparation	Typically affects males, but rarely females are also affected Ethnicity of equatorial origin
Echinocytes	PK deficiency Other glycolytic enzyme deficiency	PK enzyme activity Quantify activity of other glycolytic enzymes	Autosomal recessive, likely to have no family history
Schistocytes	DIC and/or perinatal asphyxia	Low levels of FV and FVIII, elevated levels of D-dimers	Low or falling platelet count Normal to high IPF
	Heinz body HA	Positive result of Heinz body preparation	Normal to high MPV DIC, perinatal asphyxia
	ADAMTS-13 deficiency (TTP)	Severely decreased ADAMTS-13 activity (<0.1 U/mL) high levels of LDH	ADAMTS-13 deficiency, early neonatal HUS, and giant hemangiomas all involve platelet consumption from endothelial injury and all have a similar neonatal presentation
	Neonatal hemolytic-uremic syndrome	Acute renal failure	
	Homozygous protein C deficiency	Severely decreased functional protein C activity (<1%)	
	Giant hemangioma	May be internal or external	

DAT, Direct antiglobulin test; DIC, disseminated intravascular coagulation; EMA, eosin 5-maleimide; FV, factor V; FVIII, factor VIII; G6PD, glucose-6-phosphate dehydrogenase; HA, hemolytic anemia; HUS, hemolytic uremic syndrome; IPF, immature platelet fraction; LDH, lactic dehydrogenase; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PK, pyruvate kinase; TTP, thrombotic thrombocytopenic purpura.
From Christensen RD, Yaish HM. Hemolytic disorders causing severe neonatal hyperbilirubinemia. *Clin Perinatol*. 2015;42:515–527. Table 3.

Table 139.3 Syndromes Associated with Congenital Hyporegenerative Anemia

SYNDROME	PHENOTYPIC FEATURES	GENOTYPIC FEATURES
Adenosine deaminase deficiency	Autoimmune hemolytic anemia, reduced erythrocyte adenosine deaminase activity	AR, 20q13.11
Congenital dyserythropoietic anemias	*Type I (rare):* megaloblastoid erythroid hyperplasia and nuclear chromatin bridges between nuclei *Type II (most common):* hereditary erythroblastic multinuclearity with positive acidified serum test result, increased lysis to anti-I antibodies *Type III:* erythroblastic multinuclearity ("gigantoblasts"), macrocytosis	*Type I:* 15q15.1-q15.3 *Type II:* 20q11.2 *Type III:* 15q21
Diamond-Blackfan syndrome	Steroid-responsive hypoplastic anemia, often macrocytic after 5 mo of age	AR; sporadic gene variants and AD inheritance described; 19q13.2, 8p23.3-p22
Dyskeratosis congenita	Hypoproliferative anemia usually presenting between 5 and 15 yr of age	X-linked recessive, locus on Xq28; some cases with AD inheritance
Fanconi syndrome	Steroid-responsive hypoplastic anemia, reticulocytopenia, some macrocytic RBCs, shortened RBC life span Cells are hypersensitive to DNA cross-linked agents	AR, multiple genes: complementation; group A 16q24.3; group B Xp22.3; group C 9q22.3; group D2 3p25.3; group E 6p22-p21; group F 11p15; group G 9p13
Osler hemorrhagic telangiectasia syndrome	Hemorrhagic anemia	AD, 9q34.1
Osteopetrosis	Hypoplastic anemia from marrow compression; extramedullary erythropoiesis	AR, 16p13, 11q13.4-q13.5; AD, 1p21; lethal, reduced levels of osteoclasts
Pearson syndrome	Hypoplastic sideroblastic anemia, marrow cell vacuolization	Pleioplasmatic rearrangement of mitochondrial DNA; X-linked or AR
Peutz-Jeghers syndrome	Iron-deficiency anemia from chronic blood loss	AD, 19p13.3
ATR-X and ATR-16 syndromes	ATR-X: hypochromic, microcytic anemia; mild form of hemoglobin H diseaseATR-16: more significant hemoglobin H disease and anemia are present	ATR-16, 16p13.3, deletions of α-globin locus

AD, Autosomal dominant; AR, autosomal recessive; ATR-16, chromosome 16–related α-thalassemia/mental retardation; ATR-X, X-linked α-thalassemia/mental retardation.
From Christensen RD. Neonatal erythrocyte disorders. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*. 10th ed. Philadelphia: Elsevier; 2018: Table 81-2.

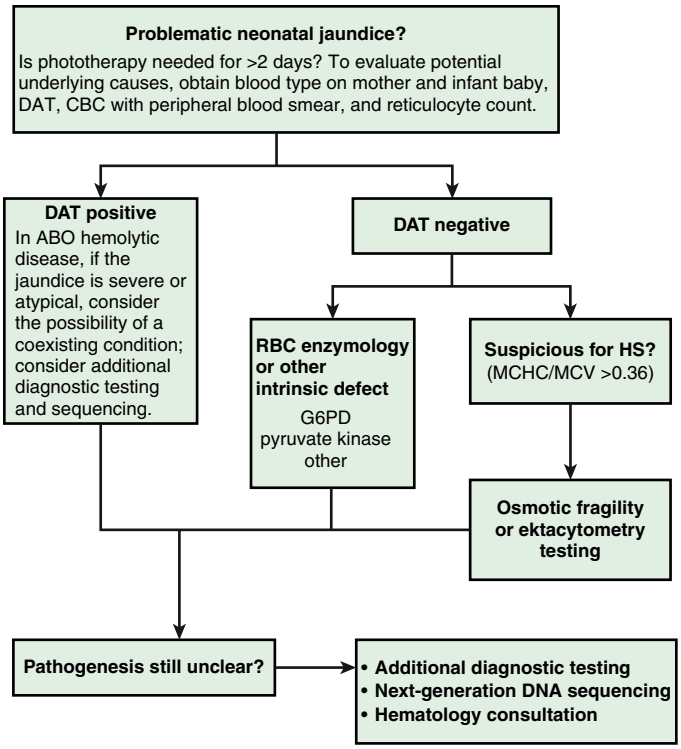

Fig. 139.4 Algorithm for the evaluation of the neonate with problematic jaundice of unclear cause. Not all neonates who receive phototherapy for 2 days or more have hemolytic jaundice. However, if hemolytic jaundice is suspected, this algorithm for stepwise evaluation of the cause might be useful. DAT, Direct antiglobulin test; G6PD, glucose 6-phosphate dehydrogenase; HS, hereditary spherocytosis; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume. (*From Christensen RD. Neonatal erythrocyte disorders. In Gleason CA, Juul SE, eds. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018: Fig. 81-15.*)

to older children, including celiac disease or menstrual bleeding. Diagnosis and treatment of hemorrhage in the newborn period are discussed in Chapter 142.

Fetomaternal hemorrhage (FMH) is caused by abnormal bleeding from fetal to maternal circulation before or during delivery. Although small amounts of FMH can be normal, more substantial pathologic FMH (>30 mL of fetal blood) occurs in 3 per 1,000 births. In comparison, large (>80 mL) or massive (>150 mL) FMH occurs in 0.9 and 0.2 per 1,000 births, respectively. Clinical signs of FMH vary due to differential fetal compensation. Decreased or absent fetal movement is the most common antenatal presentation and should prompt clinical suspicion. Postnatally, infant pallor, tachycardia, hypotension, and poor perfusion can indicate clinically significant anemia.

A standard diagnostic modality for FMH is the Kleihauer-Betke test, which leverages the differential stability of HbF vs HbA on acid exposure to identify fetal erythrocytes in the maternal circulation from a maternal blood smear (Fig. 139.5). However, this test requires technical skill, expert interpretation, and may not be available in a timely manner. Some laboratories now offer flow cytometry–based assays to quantify fetal RBCs in maternal circulation.

ANEMIA MANAGEMENT PRINCIPALS

Red Blood Cell Transfusions

The decision to transfuse packed RBC for anemia depends on the severity of symptoms, the hemoglobin concentration, and the presence of comorbidities that can alter oxygen delivery, such as pulmonary hypertension, bronchopulmonary dysplasia, cyanotic congenital heart disease, or other respiratory pathology. Benefits should be balanced against risks, including volume overload, hemolytic and nonhemolytic reactions, exposure to blood product preservatives and toxins, graft-versus-host reaction, and transfusion-acquired infections such as

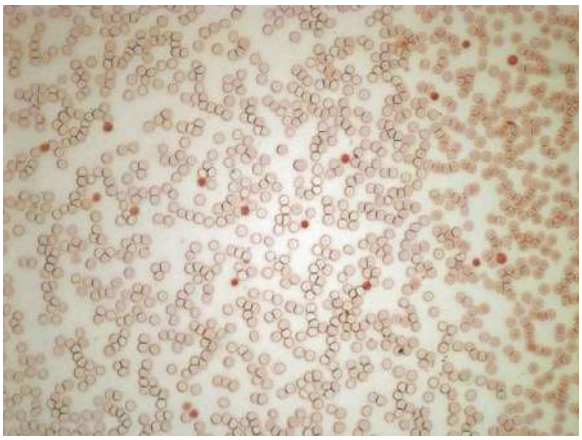

Fig. 139.5 Acid elution technique of Kleihauer (Kleihauer-Betke test). Fetal red blood cells stain with eosin and appear dark. Adult RBCs do not stain and appear as "ghosts." (*From Liley HG, Gardener G, Lopriore E, Smits-Wintjens V. Immune hemolytic disease. In Orkin SH, Nathan DG, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier; 2015: Fig. 3-2.*)

Table 139.4 Suggested Transfusion Thresholds

	PRESENCE OF RESPIRATORY SUPPORT	ABSENCE OF RESPIRATORY SUPPORT
POSTNATAL AGE	HEMOGLOBIN CONCENTRATION g/dL (HEMATOCRIT %)	
Week 1	11.0 (33%)	10.0 (30%)
Week 2	10.0 (30%)	8.5 (25%)
Week 3	8.5 (25%)	7.0 (21%)

Values based on thresholds described in Kirpalani H, Bell EF, Hintz SR, et al. Higher or lower hemoglobin transfusion thresholds for preterm infants. *N Engl J Med.* 2020;383(27):2639–2651.

CMV, HIV, parvovirus, hepatitis B, and hepatitis C (see Chapter 523). Transfusion decisions should also consider the time course in which anemia developed, whether ongoing blood loss or hemolysis are anticipated, and if there are any planned surgical interventions.

Many neonates in the NICU require RBC transfusions, particularly among premature and very low birthweight (VLBW) infants. Several trials to compare restrictive (lower) to liberal (higher) transfusion thresholds have shown no significant differences in death or serious morbidity, with restrictive thresholds modestly reducing blood product exposure. These studies provide the basis for neonatal transfusion guidelines based on postnatal age and respiratory support needs (Table 139.4). *In full-term anemic infants, RBC transfusions should be similarly based on hemodynamic stability, respiratory status, clinical status, and expected clinical trajectory.*

To reduce blood product-associated CMV transmission to vulnerable infants, it is important that transfused RBCs are leukocyte reduced or CMV seronegative. There remains a small risk of transfusion-associated graft versus host disease even after RBC irradiation. Although data do not support specific transfusion volumes, the typical range is from 10-20 mL/kg. Infants at risk of volume overload, including neonates with congenital cardiac disease or who were born in the setting of chronic abruption, are typically given smaller volume transfusions (often 5 mL/kg). *One logical goal of RBC transfusions is to target a specific goal hemoglobin concentration.* Each 5 mL/kg of transfused RBCs is expected to raise the hemoglobin concentration by 1 g/dL.

Transfusion of RBCs is typically delivered at a rate of 3-5 mL/kg/hr, with a slower rate preferred for very small, acutely ill infants with a tenuous fluid status. Each transfusion should be completed within 4 hours, or before a given blood product expires.

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Chapter 140

Hemolytic Disease of the Fetus and Newborn

Christopher S. Thom and Michele P. Lambert

Hemolytic disease of the fetus and newborn (HDFN), also known as **erythroblastosis fetalis**, is a broad diagnosis that applies to any fetus or neonate who develops alloimmune hemolysis caused by the transplacental passage of maternal antibodies directed against paternally derived red blood cell (RBC) antigens. Although more than 60 different RBC antigens can elicit a maternal antibody response, clinically significant disease is most often associated with incompatibility in ABO blood groups or rhesus (Rh) antigen (Table 140.1). HDFN caused by anti-RhD antibodies, occurring in RhD-positive infants born to RhD-negative mothers, is the most severe form because of the highly immunogenic nature of the RhD antigen. Less frequently, hemolytic disease may be caused by differences in other Rh system antigens, or by other RBC antigens such as C^W, C^X, D^U, K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. *Early recognition and diagnosis facilitate timely interventions to prevent adverse sequelae.*

HDFN CAUSED BY Rh INCOMPATIBILITY

Pathogenesis

Rh antigenic determinants are genetically transmitted from each parent and determine Rh blood type by directing the production of Rh C, c, D, E, or e proteins to be expressed on the RBC surface. RhD alloimmunization is responsible for 90% of HDFN cases involving the Rh antigen system, but other Rh antigens, particularly E and c, can be causal. Rh sensitization usually occurs in the first pregnancy when small amounts of blood (usually >1 mL) enter maternal circulation so that most instances of sensitization occur around the time of delivery. Although sensitization may occur earlier in the first pregnancy resulting in some hemolysis, HDFN rarely occurs during a first pregnancy. After sensitization, smaller doses of antigen can stimulate antibody production, so all subsequent infants expressing the cognate antigen are at risk for HDFN. For this reason, the severity of HDFN also typically worsens with successive pregnancies. *Routine administration of Rh immunoglobulin (RhoGAM) to mothers at risk for Rh alloimmunization, both at 28 and 32 weeks' gestation and within 72 hours after delivery of Rh-positive infants, has reduced initial sensitization to an estimated <0.1% of at-risk pregnancies in high-income countries.*

Clinical Manifestations

The severity of HDFN is variable, ranging from mild hemolysis without overt symptoms to severe anemia with compensatory hyperplasia of erythropoietic tissues, including massive hepatosplenomegaly. When hemolysis exceeds the compensatory regenerative capacity of the hematopoietic system, profound anemia, thrombocytopenia, coagulopathy, cardiomegaly, respiratory distress, massive anasarca, and circulatory collapse can result. Perinatal hemoglobin concentrations may be as low as 3-4 g/dL.

HDFN can also cause abnormal fluid collection in two or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), a clinical scenario termed **hydrops fetalis,** which frequently results in significant clinical morbidity or death in utero or shortly after birth. Hydrops results from heart failure along with subsequent hepatic congestion and dysfunction. This leads to reduced serum albumin and loss of intravascular oncotic pressure. Consequent edema can lead to extravascular fluid accumulation in the lungs (pleural effusion), abdomen (ascites), and elsewhere, which can compromise ventilation and lead to a range of life-threatening complications (Fig. 140.1). Hydrops is typically present when the fetal hemoglobin level is <5 g/dL but can occur when hemoglobin levels are between 7 and 9 g/dL. Hydrops does not invariably occur with low hemoglobin concentration, instead depending on the duration of anemia and the gestational age when anemia developed.

Infants affected by HDFN may not be jaundiced at birth because of effective placental clearance of lipid-soluble unconjugated bilirubin. However, in severe cases, bilirubin pigments can stain the amniotic fluid, cord, and vernix. In either case, hyperbilirubinemia is generally evident within 24 hours of birth, as hemolysis overwhelms the infant's bilirubin clearance system. Extremely high levels of unconjugated bilirubin levels present a risk of bilirubin encephalopathy **(kernicterus)**, which is worsened in patients with concomitant hypoxia or acidosis.

Hypoglycemia may further complicate clinical management of infants with severe HDFN. This may be related to islet cell hypertrophy and hyperinsulinism due to growth stimulatory effects of anti-RhD antibodies on the pancreas.

Table 140.1 Etiologies of Hemolytic Disease of the Fetus and Newborn

	Rh	ABO	KELL
BLOOD GROUPS			
Mother	Rh-negative	O (occasionally B)	K1-negative
Infant	Rh-positive (D is most common)	A (sometimes B)	K1-positive
CLINICAL FEATURES			
Occurrence in firstborn	5%	40–50%	Rare
Severity in subsequent pregnancies:	Predictable	Difficult to predict	Somewhat predictable
Stillbirth/hydrops	Frequent (less with Rh-immunoglobulin use)	Rare	10%
Severe anemia	Frequent	Rare	Frequent
Jaundice	Prominent, severe	Mild-moderate	Mild
LABORATORY TESTS			
Direct antiglobulin test (infant)	Positive	Positive or negative	Positive or negative
Reticulocyte count	Elevated	Elevated	Variable
RBC antibodies (mother)	Usually detectable Antibody titers may help predict severity of fetal disease	May not be detectable Antibody titers may not correlate with fetal disease	Usually detectable Antibody titers may not correlate with fetal disease; fetus can be affected at titers lower than for Rh-mediated hemolysis

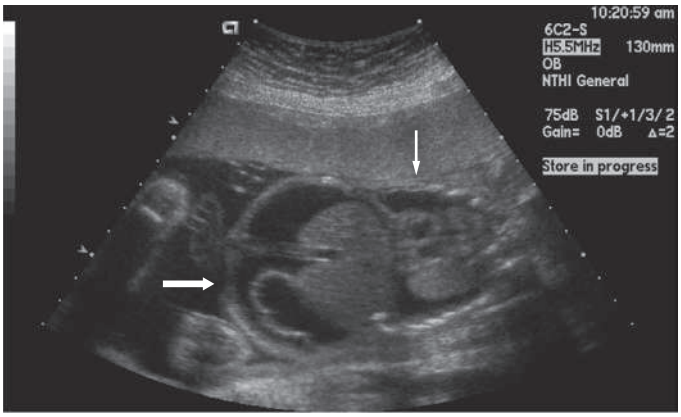

Fig. 140.1 Hydrops fetalis. Longitudinal sonographic image of the fetus, with ascitic fluid outlining the liver *(large arrow)*. The *small arrow* shows pleural effusion above the diaphragm. *(From Wilkins I: Nonimmune hydrops. In Creasy RK, Resnick R, Iams JD, et al., eds. Creasy & Resnik's Maternal-Fetal Medicine. 7th ed. Philadelphia: Elsevier; 2014: Fig. 37-2.)*

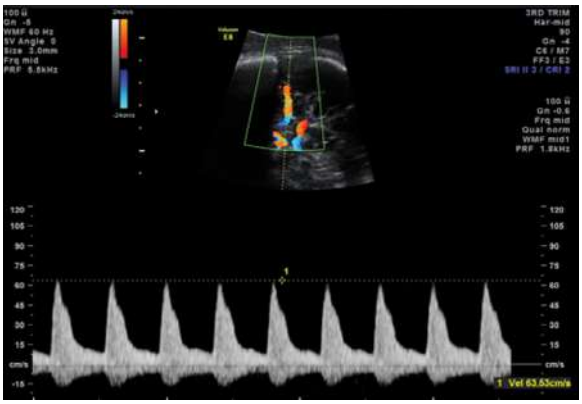

Fig. 140.2 Middle cerebral artery (MCA) Doppler study of elevated peak systolic velocity (PSV). MCA-PSV can predict fetal anemia with sufficient accuracy to determine management, including the need for intrauterine transfusion or, in the mid to late third trimester, early delivery. Fetal hemoglobin is typically measured at the start and end of intravascular transfusion to validate the prediction from MCA-PSV results. The reliability of MCA-PSV can decrease after intrauterine transfusion because of the altered rheostatic characteristics of transfused adult blood. This is now the method of choice for detecting fetal anemia. *(From Liley HG, Gardener G, Lopriore E, Smits-Wintjens V. Immune hemolytic disease. In Orkin SH, Nathan DG, Ginsburg D, et al., eds. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 8th ed. Philadelphia: Elsevier' 2015: Fig. 3-6.)*

Diagnosis, Prevention, and Treatment

Definitive diagnosis of HDFN requires demonstration of blood group incompatibility between mother and infant, and corresponding maternal antibody bound to the infant's RBCs. However, severe clinical presentations strongly suggest the diagnosis. Emergent interventions may be required before definitive test results become available.

During pregnancy, expectant parents should have blood tested for potential blood type incompatibility, including ABO and Rh antigens. If RhD incompatible, maternal anti-RhD IgG titers should be measured early in pregnancy. Paternal blood can be tested to determine the fetal risk of inheriting the cognate antigen, typically either 50% or 100% depending on whether the father is heterozygous or homozygous. However, as paternal serologic testing alone is not fully accurate, molecular genotyping may be recommended for both parents.

Fetal genotyping provides an accurate prediction for the development of HDFN in sensitized mothers. Fetal Rh status is available by isolating fetal cells or cell-free fetal DNA from the maternal circulation. These methods are replacing amniocentesis and chorionic villus sampling methods and associated risks. Elevated antibody titers, or rising titers, correspond to increased HDFN risk.

Without Rh immunoglobulin prophylaxis, any Rh-negative woman with a previous pregnancy or abortion, prior exposure to transfused blood products, or receipt of an organ transplant is at risk for Rh sensitization. If a mother has had a previously affected infant or stillbirth, the Rh-positive infant is usually equally or more severely affected than the previous infant. Although there can be poor correlation between the anti-RhD titer level and disease severity, Rh-negative mothers found to have RhD antibody titers of ≥1:16 (15 IU/mL in Europe) at any time during a subsequent pregnancy warrant close monitoring for fetal anemia.

Pregnancies at risk for HDFN should be managed by maternal-fetal specialists. In some cases, monitoring must begin at 16-24 weeks' gestation. This is typically done via noninvasive Doppler ultrasonography of middle cerebral artery (MCA) flow velocity, which can be used to monitor for increased vascular resistance in fetal arteries indicative of **fetal anemia** (Fig. 140.2). Moderate to severe anemia increases MCA blood flow, so peak MCA flow velocity can be a quantitative correlate for anemia severity. Real-time ultrasound is used to detect signs of hydrops (skin or scalp edema, pleural or pericardial effusions, and ascites) and fetal heart rate monitoring. Early ultrasonographic signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. *In the setting of concerning ultrasonographic findings, percutaneous umbilical blood sampling (PUBS) can provide more direct assessment of fetal hemoglobin level and facilitate intrauterine transfusions.*

Although cord blood hemoglobin content typically varies in proportion to disease severity, hemoglobin may be within the normal range due to compensatory bone marrow and extramedullary hematopoiesis. Reticulocytosis will be present and a peripheral blood smear will show polychromasia with abundant nucleated RBCs. Thrombocytopenia may develop in severe cases. Umbilical cord bilirubin levels are generally between 3 and 5 mg/dL, including elevated direct bilirubin levels from cholestasis. Indirect-reacting bilirubin content rises rapidly in the first 6-12 hours of life.

Indications for delivery include fetal distress, complications during in utero interventions, and pulmonary maturity. Many affected infants are delivered preterm due to concerns for fetal well-being, after balancing risks of prematurity. The birth should be attended by a skilled neonatal resuscitation team familiar with the infant's prenatal course. *Because severe hemolytic anemia can cause rapid cardiovascular compromise, a team skilled in evaluation in management of HDFN should be involved when the diagnosis is suspected or confirmed, especially when there is a history of prior infants affected by HDFN.* Small packed RBC (PRBC) transfusions can be used to partially correct anemia, although volume expansion (e.g., large transfusions) risks worsening cardiac failure. Phototherapy may be necessary to treat hyperbilirubinemia in the first 24 hours of life if bilirubin levels exceed safe limits on an age-based nomogram (see Chapter 137). Although it is the indirect bilirubin fraction that crosses the blood-brain barrier to cause kernicterus, clinical decision-making is often based on total serum bilirubin levels.

Despite adequate resuscitation, phototherapy, and/or other empiric treatments, some infants with HDFN require exchange transfusions to treat anemia and/or hyperbilirubinemia. The decision to proceed with exchange transfusion is typically based on clinical status and trajectories in hemoglobin or serum bilirubin values, specifically the likelihood that serum bilirubin, plotted against postnatal hours of life, will reach a dangerous level (see Chapter 137). Signs and symptoms of kernicterus are absolute indications for exchange transfusion. Previous kernicterus or severe HDFN in a sibling, severe reticulocytosis >15%, or prematurity (with increased kernicterus risk) are additional factors to be considered in the decision to proceed with exchange transfusion (see Chapter 137).

Complications related to HDFN can also present weeks after birth, irrespective of the prenatal or perinatal course. Late anemia can present after 4-6 weeks of life, sometimes clinically manifesting as poor feeding or growth. This can result from ongoing hemolysis caused by persistent circulating maternal alloantibodies, or from hyporegenerative anemia caused by suppression of bone marrow erythropoiesis. These etiologies can be distinguished by reticulocyte count and bilirubin level, with ongoing hemolysis driving reticulocytosis and hyperbilirubinemia.

Neutropenia may also be observed in association with hyporegenerative anemia. Outpatient blood and reticulocyte counts should be monitored serially under the supervision of an expert hematologist to determine the need for interventions through bone marrow recovery. Iron supplementation or erythropoietin therapy can be helpful. In some cases, PRBC transfusions can be required for months after birth, until the infant's own erythropoietic system becomes more robust.

Hemolysis and hyperbilirubinemia can also cause late-onset complications. Jaundice typically resolves spontaneously within a few weeks or months with conservative management. Portal vein thrombosis and portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. This complication is thought to be seen in infants with prolonged, traumatic, or septic umbilical vein catheterization. Inspissated bile syndrome is another rare complication, associated with persistent icterus and significant elevations in both direct and indirect bilirubin levels.

The outcome for Rh-incompatible fetuses varies greatly, depending on the characteristics of both the RBC antigen and the maternal antibodies. Although fetal transfusions and prenatal interventions can ameliorate some complications, those with severe hydrops remain at risk for cerebral palsy, developmental delay, and deafness, requiring medical and procedural interventions for hydrops prenatally or after birth. Infants should be monitored closely for late complications by pediatric hematologists in the outpatient setting.

HDFN CAUSED BY ABO INCOMPATIBILITY

ABO incompatibility is the most common cause of HDFN, with approximately 20% of live births at theoretical risk. Of at-risk infants, clinical manifestations develop in 1–10% and are usually less severe than Rh disease, rarely requiring aggressive clinical management or therapeutic intervention aside from phototherapy. This is because naturally occurring maternal antibodies against ABO blood group antigens are mostly IgM and therefore do not cross the placenta. However, some group O mothers will naturally produce anti-A or anti-B IgG antibodies that can cross the placenta to cause immune-mediated hemolysis. For this reason, ABO incompatibility can cause hemolysis even in a firstborn infant. Another reason for mild disease manifestations is that fetal and neonatal RBCs have relatively low ABO expression, limiting binding sites for maternal antibodies.

Clinical Manifestations

Affected infants will typically develop jaundice in the first day of life. Severe clinical manifestations, such as hydrops, severe anemia, or hepatosplenomegaly, are rare. Diagnosis requires serologic ABO incompatibility between the mother and infant, a positive DAT, and hyperbilirubinemia with or without anemia. Affected infants often have mild anemia and reticulocytosis, with peripheral blood smears showing polychromasia, nucleated RBCs, and spherocytes. *Phototherapy may be required based on bilirubin level and postnatal age, and is typically effective in lowering serum bilirubin levels* (see Chapter 137). In some cases, hemolysis can persist for weeks until maternal antibodies are cleared. Intravenous immunoglobulin (IVIG) administration can help to limit hemolysis and potentially avoid exchange transfusion and/or PRBC transfusions in cases with dangerous levels of hyperbilirubinemia or anemia, respectively. Rarely, affected infants who also have hyporegenerative anemia can require PRBC transfusions several weeks after birth. For this reason, outpatient monitoring is essential for newborns with ABO hemolytic disease. However, the persistence of hemolytic anemia or spherocytosis beyond 2 weeks of age can indicate an alternative diagnosis, such as hereditary spherocytosis (see Fig. 139.3).

OTHER ETIOLOGIES OF HDFN

Incompatibility in blood group antigens other than Rh or ABO account for <5% of HDFN. Minor RBC antigen mismatch is emerging as a common cause of HDFN in the developed countries in which anti-RhD immune globulin is routinely used. The likelihood of minor antigen mismatches is a function of population frequency, antigen surface density on RBCs, and immunogenicity in the mother. In most cases, the infant's direct antiglobulin test (DAT) will be positive and maternal serum will have alloantibodies against infant (and paternal) erythrocytes. Elution techniques can identify the antigen specificity.

Common RBC antigens that can lead to clinically relevant incompatibility include those in the Kell, Duffy, and MNS blood groups. Kell incompatibility can be the most clinically relevant, as the severity of the hemolytic anemia is difficult to predict based on previous obstetric history, amniotic fluid bilirubin determinants, or maternal antibody titer (Table 140.2). Kell-alloimmunized infants often have inappropriately low numbers of circulating reticulocytes caused by erythroid suppression, and even low maternal titers of anti-Kell antibodies may cause significant anemia due to loss of precursors expressing the antigen as well as mature erythrocytes. No pharmacologic therapies are available to prevent sensitization with these minor antigens. As with cases of Rh and ABO incompatibility, treatment is supportive, including exchange transfusion for severe presentations.

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Table 140.2 Red Cell Antigens That Cause Hemolytic Disease of the Fetus and Newborn (HDFN)

MILD HDFN	MODERATE HDFN	SEVERE HDFN
ABO (A, B)	Rh (EW, hrs, Tar, Rh32, HrBE, Hr_o)	Rh (D, c, f, Ce, C^w, cE)
Rh (C, e, C^x, VS, CE, Be^a, JAL)	Diego (Di^a, Di^b, Wr^a, ELO)	Kell (K, k, Ku, Js^b)
Kell (Kp^a, Js^a, Ul^a)	Duffy (Fy^a)	Globoside (PP_1P_k)
Junior (Jra)	Gerbich (Ge3)	MNSs (Vw, Mur, MUT)
Kidd (Jk^a, Jk^b, Jk3)	H (H)	Mittenberger (Mi^a)
Duffy (Fy^b)	Kell (K, k, Ku, Js^b)	MNSs (Vw, Mur, MUT)
Langereis (Lan)	MNSs (U, Ss S, s, Mt^a, M^v)	Gerbich (PP1Pk)
MNSs (M, N, Hil, Or)	Colton (Co^a)	(HJK)
Colton (Co^b, Co^3)	(Kg)	—
Scianna (Rd, SC2)	(Sara)	—
Xg (Xg^a)	—	—
(At^a)	—	—

Mild HDFN, published reports of needing phototherapy for postnatal jaundice; *moderate HDFN*, published reports of needing postnatal exchange transfusion; *severe HDFN*, published reports of hydrops fetalis or intrauterine transfusions.
Note that some antigens have no system as per International Society of Blood Transfusion classification.
From Jackson ME, Baker JM. Hemolytic disease of the fetus and newborn. *Clin Lab Med.* 2021;41:133–151. Table 1.

Chapter 141

Neonatal Polycythemia

Christopher S. Thom and Michele P. Lambert

Neonatal polycythemia is broadly defined as an elevated hemoglobin or hematocrit level. This can be due to primary myeloproliferative disorders (e.g., polycythemia vera) or reactive processes, such as from chronic hypoxemia or living at high altitudes.

In infants, polycythemia is inferred from a hematocrit level >2 standard deviations above the normal value for gestational and postnatal age (Figs. 138.2 and 139.1). Full-term infants are therefore considered polycythemic with a hemoglobin level above ~22 g/dL or hematocrit >65%. It is important that these values are obtained from a "central" venous or arterial puncture, as heelstick or capillary samples can report artificially elevated values. Due to fluid shifts in the newborn period, hematocrit levels typically peak at 2-3 hours of life.

Although most polycythemic individuals are asymptomatic, symptomatic blood **hyperviscosity** from polycythemia can cause sluggish blood flow that decreases tissue perfusion and leads to metabolic disturbances. Signs and symptoms are vague, including irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Thus a high index of suspicion is often required for diagnosis and coincident respiratory, cardiovascular, and neurologic disorders should be investigated. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis (NEC), renal vein thrombosis, and renal failure in newborns. Related symptoms often appear in the first hours of life but can be delayed by up to 2-3 days depending on clinical context.

Dehydration should be considered as a potential contributing cause in symptomatic polycythemic infants. Neonatal polycythemia can also result from processes that lead to passive RBC transfusion into the fetus or increased intrauterine erythropoiesis. Passive fetal RBC transfusions may occur from prolonged delayed umbilical cord clamping but can also present in recipients of twin-twin transfusions or unrecognized maternal-fetal transfusions from the placenta.

Most cases of increased fetal erythropoiesis are thought to result from chronic intrauterine hypoxia, which stimulates erythropoietin and RBC production. Increased fetal erythropoiesis is associated with polycythemia in postterm (3%) and term (1–2%) infants; small-for-gestational-age (8%) or large-for-gestational-age (3%) infants; infants of diabetic mothers; infants of hypertensive mothers or those taking propranolol; and infants with trisomy 13, 18, or 21, adrenogenital syndrome, neonatal Graves disease, hypothyroidism, or Beckwith-Wiedemann syndrome. Delayed cord clamping does not increase the incidence of polycythemia. Contraindications to delayed cord clamping include suspected chronic intrauterine hypoxia (e.g., severe growth restriction) and maternal diabetes, which independently increase RBC production. The frequency of neonatal polycythemia is also increased for births at higher altitudes (5% at high altitude vs 1–2% at sea level).

Asymptomatic polycythemia can be treated conservatively, with consideration for supplemental enteral or intravenous hydration. Treatment for symptomatic infants should also begin with supplemental hydration, after considering potential comorbidities (e.g., heart failure). All polycythemic infants should have intake and output, blood glucose, and bilirubin levels followed closely. Infants with hyperviscosity symptoms may benefit from partial exchange transfusions, particularly if the hematocrit reaches ≥75% and symptoms worsen despite aggressive intravenous hydration.

Outcomes are more closely determined by etiologies contributing to chronic intrauterine hypoxia than polycythemia per se. Although infants treated with partial exchange transfusion may be at increased risk of NEC, it is unclear whether adverse long-term speech, fine motor, cognitive, and behavioral outcomes are affected.

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Chapter 142

Hemorrhage in the Newborn Infant

Christopher S. Thom and Michele P. Lambert

Congenital and acquired bleeding disorders can manifest at varying times in infants and older children. Hemorrhage in an otherwise healthy newborn may suggest an inherited coagulation defect (e.g., hemophilia) or concurrent thrombocytopenia. Bleeding in otherwise sick neonates is frequently caused by underproduction or consumption of coagulation factors and/or platelets. Common acquired hemorrhagic disorders include hemorrhage due to vitamin K deficiency (see Chapter 71 and below), disseminated intravascular coagulation (DIC: see Chapter 532), or immune-mediated thrombocytopenia (see Chapter 533).

The neonatal hemostatic system differs from older children and adults. This impacts bleeding risk and laboratory assessment, and should enter into management considerations. Plasma levels of vitamin K–dependent coagulation factors (II, VII, IX, X, protein C, protein S) and antithrombin are initially low at birth and do not reach adult ranges until approximately 6 months of age. Note that overall the neonatal hemostatic system tends toward hypercoagulability, given low levels of protein C, protein S, and antithrombin. This may explain why neonatal platelets are hypofunctional in response to some agonists, and why neonatal platelet content differs from adults (Chapters 525 and 526).

HEMORRHAGIC DISEASE OF THE NEWBORN

Bleeding from vitamin K deficiency, otherwise known as **hemorrhagic disease of the newborn**, results from transient but profound deficiencies in vitamin K–dependent coagulation factors. Vitamin K normally facilitates carboxylation of factors II, VII, IX, and X, which is necessary for enzymatic activities. Decarboxylated factors are biologically inactive. Without vitamin K, decarboxylated *proteins induced in vitamin K absence (PIVKA)* are secreted. The classic form of this disease can be prevented with intramuscular injection of vitamin K (phytonadione) just after birth.

The disease process most often affects exclusively breastfed infants who did not receive intramuscular vitamin K prophylaxis at birth. Maternal breastmilk lacks free vitamin K, and newborns lack the intestinal flora normally responsible for vitamin K synthesis. Premature infants with nutritional deficiencies are also at risk of vitamin K deficiency and bleeding.

Laboratory testing typically reveals prolonged prothrombin time (PT) and partial thromboplastin time (PTT) in affected infants, with low plasma levels of prothrombin (II) and factors VII, IX, and X. Soluble **PIVKA** measurement can also act as a laboratory marker for vitamin K status. Factors V and VIII, fibrinogen, bleeding time, clot retraction, platelet count, and platelet function will be within normal newborn ranges.

Intramuscular administration of 1 mg vitamin K_1 (phytonadione) soon after birth can prevent bleeding complications from vitamin K deficiency in most full-term infants. Low birthweight infants may be given 0.5 mg phytonadione, although weight-based dosing varies between institutions. Phytonadione is the only form of vitamin K available in the United States. Vitamin K_2, also known as menaquinones, constitutes a minority of the vitamin K consumed by humans or produced by intestinal flora. Vitamin K prophylaxis does not prevent all hemorrhagic disease of the newborn. Although rare, cases can occur in full-term infants, preterm infants with significant nutritional deficiencies, and infants with malabsorption.

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Chapter 142

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The neonatal hemostatic system differs from older children and adults. This impacts bleeding risk and laboratory assessment, and should enter into management considerations. Plasma levels of vitamin K–dependent coagulation factors (II, VII, IX, X, protein C, protein S) and antithrombin are initially low at birth and do not reach adult ranges until approximately 6 months of age. Note that overall the neonatal hemostatic system tends toward hypercoagulability, given low levels of protein C, protein S, and antithrombin. This may explain why neonatal platelets are hypofunctional in response to some agonists, and why neonatal platelet content differs from adults (Chapters 525 and 526).

HEMORRHAGIC DISEASE OF THE NEWBORN

Bleeding from vitamin K deficiency, otherwise known as **hemorrhagic disease of the newborn**, results from transient but profound deficiencies in vitamin K–dependent coagulation factors. Vitamin K normally facilitates carboxylation of factors II, VII, IX, and X, which is necessary for enzymatic activities. Decarboxylated factors are biologically inactive. Without vitamin K, decarboxylated *proteins induced in vitamin K absence (PIVKA)* are secreted. The classic form of this disease can be prevented with intramuscular injection of vitamin K (phytonadione) just after birth.

The disease process most often affects exclusively breastfed infants who did not receive intramuscular vitamin K prophylaxis at birth. Maternal breastmilk lacks free vitamin K, and newborns lack the intestinal flora normally responsible for vitamin K synthesis. Premature infants with nutritional deficiencies are also at risk of vitamin K deficiency and bleeding.

Laboratory testing typically reveals prolonged prothrombin time (PT) and partial thromboplastin time (PTT) in affected infants, with low plasma levels of prothrombin (II) and factors VII, IX, and X. Soluble **PIVKA** measurement can also act as a laboratory marker for vitamin K status. Factors V and VIII, fibrinogen, bleeding time, clot retraction, platelet count, and platelet function will be within normal newborn ranges.

Intramuscular administration of 1 mg vitamin K_1 (phytonadione) soon after birth can prevent bleeding complications from vitamin K deficiency in most full-term infants. Low birthweight infants may be given 0.5 mg phytonadione, although weight-based dosing varies between institutions. Phytonadione is the only form of vitamin K available in the United States. Vitamin K_2, also known as menaquinones, constitutes a minority of the vitamin K consumed by humans or produced by intestinal flora. Vitamin K prophylaxis does not prevent all hemorrhagic disease of the newborn. Although rare, cases can occur in full-term infants, preterm infants with significant nutritional deficiencies, and infants with malabsorption.

Table 142.1 Vitamin K Deficiency Bleeding (Hemorrhagic Disease of the Newborn)

	EARLY-ONSET DISEASE	CLASSIC DISEASE	LATE-ONSET DISEASE
Age	0-24 hr	2-7 days	1-6 mo
Potential sites of hemorrhage	Cephalohematoma Subgaleal Intracranial Gastrointestinal Umbilicus Intraabdominal	Gastrointestinal Ear-nose-throat-mucosal Intracranial Post circumcision Cutaneous Injection sites	Intracranial Gastrointestinal Cutaneous Ear-nose-throat-mucosal Injection sites Thoracic
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K levels or absorption Inherited coagulopathy	Vitamin K deficiency Exclusive breastfeeding	Cholestasis: malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis) Abetalipoprotein deficiency Idiopathic in Asian breastfed infants Warfarin ingestion
Prevention	Avoidance of high-risk medication Possibly antenatal vitamin K to treatment of mother (20 mg) before birth and postnatal administration to infant soon after birth	Prevented by parenteral vitamin K at birth Oral vitamin K regimens require repeated dosing	Prevented by parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
Incidence	Very rare	~2% if infant not given vitamin K soon after birth	Dependent on primary disease

Infants who present with hemorrhage should be given 1-5 mg of vitamin K_1 intravenously, typically on 3 consecutive days. This regimen generally improves coagulation defects and bleeding ceases within hours. Serious bleeding, particularly in premature infants or those with liver disease, may also require intravenous transfusion of fresh-frozen plasma to correct coagulopathy. Packed RBCs (PRBCs) or whole blood transfusions may also be required to correct anemia.

Bleeding episodes most frequently occur between days of life 2 and 7. Mild bleeding may precede more severe manifestations, which are most frequently gastrointestinal, nasal, subgaleal, intracranial, or occur after circumcision.

Early-onset vitamin K deficiency bleeding can occur in the first day of life in infants born to mothers chronically treated with drugs that interfere with vitamin K absorption or function, including warfarin, phenytoin, phenobarbital, or some cholesterol-lowering medications. Usually, bleeding is promptly ameliorated by vitamin K administration, although some infants can have poor or delayed improvements in bleeding. Thus infants born to mothers who took these medications late in gestation should be given 1-2 mg intravenous vitamin K immediately after birth, and serial newborn PT monitoring should begin using cord blood. If the PT is greatly prolonged and fails to improve, or significant hemorrhage presents, fresh-frozen plasma administration can temporarily correct factor deficiencies.

Late-onset vitamin K deficiency bleeding after 2 weeks of life is most often associated with conditions that cause fat-soluble vitamin malabsorption, including cystic fibrosis, neonatal hepatitis, or biliary atresia (Table 142.1). Bleeding can be severe and is not responsive to vitamin K treatment if there is hepatocellular injury; bleeding will respond to intravenous vitamin K if there is malabsorption.

Bleeding unresponsive to vitamin K should prompt consideration for congenital clotting factor deficiencies (see Chapter 525). These conditions may present with hematomas, melena, post circumcision bleeding, or bleeding from the umbilicus. Up to 70% cases of hemophilia (factor VIII or IX deficiency) are clinically apparent in the newborn period. Congenital factor deficiency treatment requires specific factor replacement, or fresh-frozen plasma if factor concentrate is not available.

Although *oral* vitamin K administration has been investigated as an alternative to intramuscular prophylaxis, oral regimens *do not* prevent late-onset vitamin K deficiency bleeding. Thus intramuscular vitamin K prophylaxis remains the method of choice.

Prompt recognition of infants who do present with bleeding from vitamin K deficiency is critical. A presumptive diagnosis can often be made based on a complete history, even before laboratory confirmation, facilitating rapid treatment initiation. With timely therapy and supportive care, the associated mortality rate is low.

DISSEMINATED INTRAVASCULAR COAGULOPATHY

Critical illness that results in consumption of circulating coagulation factors and platelets is termed disseminated intravascular coagulation. In neonates and other patients, DIC can result in either bleeding or thrombosis. DIC occurs secondary to an array of primary processes, including but not limited to sepsis or asphyxia. Rarely, hemangiomas will cause consumption of coagulation factors and initiate this process. In addition to clinical context, coagulation studies, factor levels, and platelet counts can provide evidence of ongoing DIC. Management centers on treatment of the underlying etiology, although supportive care may include blood, plasma, vitamin K, or platelet transfusions to replace consumed factors. Usually, affected infants are critically ill, with evidence of end-organ damage. Those with DIC can have high rates of morbidity and mortality, dependent on the underlying etiology (see Chapter 532).

Diagnosis and Treatment

Diagnostic modalities for hemorrhage in neonates vary based on clinical suspicion. For example, noninvasive imaging can be used to identify hemorrhage or bleeding sequelae. Premature infants who become acutely anemic out of proportion to phlebotomy are frequently monitored for intraventricular hemorrhage or investigated for bleeding elsewhere. These diagnostic measures can help to explain the pathology leading to anemia and any related risks. In turn, diagnosis can facilitate prognostication, and in rare cases lead to potentially definitive interventions (e.g., for some vascular malformations).

Treatment for blood loss typically includes transfusion of crossmatched PRBCs, which should be given more slowly in the setting of chronic blood loss or in patients at risk of volume overload. Therapies and interventions should also focus on correcting coexisting coagulopathy and/or comorbidities that increase further bleeding risk.

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Chapter 143

Nonimmune Hydrops

Dalal Taha

Nonimmune hydrops, a significant contributor to neonatal morbidity and mortality, is the leading cause of fetal hydrops. **Hydrops fetalis** is defined by ≥2 abnormal fetal fluid collections, such as ascites, pleural, pericardial, or cutaneous edema (>5 mm) (Fig. 143.1). In addition, there may be associated placental edema (>6 mm), polyhydramnios (50%), and the rare occurrence of **mirror syndrome**, in which the mother becomes edematous. In cases in which hydrops is not caused by red cell alloimmunization, it is referred to as nonimmune hydrops. Nonimmune hydrops is the result of a range of underlying etiologies, such as high-output cardiac failure secondary to anemia or fetal arrhythmia, alterations in lymphatic development, fetal inflammation, and capillary leak or elevated central venous pressure due to structural cardiac disease. Despite advances in recognition of the underlying cause, mortality remains high with prognosis dependent on the underlying cause, degree of prematurity, and extent of disease burden at birth.

INCIDENCE AND ETIOLOGY

Estimates of incidence range between 1 in 1,700 pregnancies and 1 in 4,000 pregnancies. Population studies provide lower estimates, but this may be an underrepresentation due to a lack of information on fetuses who died in utero.

The etiologies are broad; cardiovascular, lymphatic, hematologic, and chromosomal disorders are the most common identifiable underlying causes (Table 143.1). The etiology is unknown in approximately 10–20% of cases. However, improved understanding of the lymphatic system and its contribution to the development of nonimmune hydrops has led to increased identification of the underlying etiology. Lymphatic causes of nonimmune hydrops are congenital lymphovenous atresia, in which the thoracic duct outlet is not connected to the venous circulation, and complete absence of the thoracic duct or pulmonary lymphatic perfusion syndrome, in which the pulmonary lymphatic channels abnormally conduct to the pleural space resulting in chylothorax. Other mechanisms for the development of nonimmune hydrops are not well established (Fig. 143.2).

PRENATAL DIAGNOSIS AND TREATMENT

Hydrops fetalis is identified in utero by ultrasonographic findings of excess fluid. After ruling out immune-mediated hydrops (Rh alloimmunization), other diagnostic testing may include screening for hemoglobinopathies, testing for fetal-maternal hemorrhage (Kleihauer-Betke test), and testing for infection (i.e., TORCH infections, syphilis, and parvovirus B19). Fetal echocardiography should be performed to assess for structural heart defect or arrhythmia. Commonly diagnosed causes of nonimmune hydrops in fetuses greater than 24 weeks' gestation are cardiac disorders. Amniotic fluid can be obtained for fetal genetic testing to evaluate for chromosomal and specific gene abnormalities. In cases with fetal pleural effusions, a fluid sample may be collected via thoracentesis and tested for lymphocyte count to determine whether the underlying cause of hydrops is due to lymphatic dysfunction.

In utero treatment has been successful for fetal supraventricular tachycardia (SVT), twin-twin transfusion syndrome, nonimmune fetal anemias, large vascular masses, congenital diaphragmatic hernia, and other chest occupying lesions, such as congenital cystic adenomatoid malformation (CCAM) and pulmonary sequestration. In cases in which initial ultrasound is not useful in identifying a cause, repeat ultrasound or fetal magnetic resonance imaging (MRI) can be used to reassess fetal anatomy, monitor progression of hydrops, determine an underlying diagnosis, and direct fetal intervention. The finding of nutmeg lung on fetal MRI signifies abnormal pulmonary lymphatic flow that results in chylothorax. To treat fetal pleural effusions, in the absence of an infectious etiology, fetal thoracentesis and/or thoracoamniotic shunt placement can be performed.

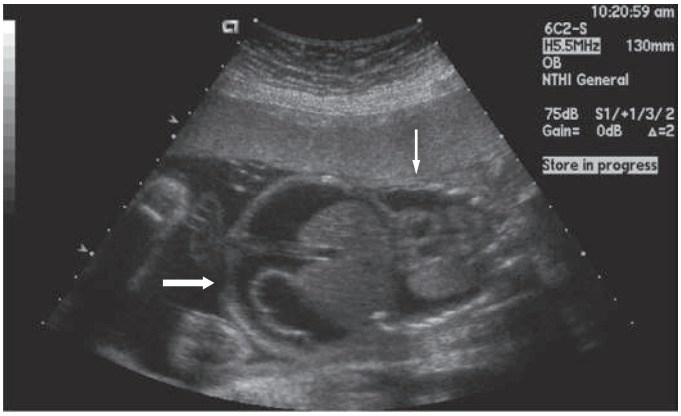

Fig. 143.1 Hydrops fetalis. Longitudinal sonographic image of the fetus, with ascitic fluid outlining the liver *(large arrow)*. The *small arrow* shows pleural effusion above the diaphragm. *(From Wilkins I. Nonimmune hydrops. In Creasy RK, Resnick R, Iams JD, et al., eds.* Creasy & Resnik's Maternal-Fetal Medicine, *7th ed. Philadelphia: Elsevier; 2014: Fig. 37-2.)*

POSTNATAL DIAGNOSIS AND TREATMENT

Postnatal therapy includes a team approach to the delivery room management that often requires immediate endotracheal tube intubation for predicted respiratory failure secondary to pleural, peritoneal, or pericardial effusions, pulmonary hypoplasia, surfactant deficiency, pulmonary edema, or poor chest wall compliance due to soft tissue edema. Immediate transfusion of packed red blood cells (RBCs) may also be required in the delivery room in the presence of anemias. Drainage of large pleural, peritoneal, or pericardial effusions may aid in achieving effective mechanical ventilation and ensure successful resuscitation. High ventilatory pressures may be needed to overcome poor chest compliance but may result in pneumothoraces or pulmonary interstitial emphysema, especially in cases with pulmonary hypoplasia.

Once the infant is stabilized, additional intensive care includes fluid and electrolyte management. Maintenance fluids should be restricted as much as possible with the goal of resolving or improving the degree of hydrops. In cases with ongoing drainage of pleural or peritoneal fluid, fluid replacement may be necessary to replete serum sodium levels and maintain hemodynamic stability. If the fluid drained is secondary to a lymphatic disorder, albumin may need to be administered to maintain adequate serum levels.

Diagnostic testing should be performed if an underlying etiology of hydrops is unknown at the time of birth to direct additional therapies. Whole exome (or genome) sequencing and microarray duplication/deletion studies are recommended to establish a diagnosis. Analysis of fluid from the pericardial, pleural, or peritoneal space may confirm an underlying lymphatic disorder if there is a lymphocyte predominance. Hypoalbuminemia and the presence of soft tissue edema is also suggestive of a lymphatic disorder. Additional evaluation of the lymphatic system includes the use of T2 weighted MRI, dynamic contrast-enhanced magnetic resonance lymphangiogram (DCMRL), and direct or conventional lymphangiogram. Interventions for congenital lymphatic disorders include ethiodized oil injection to treat pulmonary lymphatic perfusion syndrome and lymphovenous anastomosis for lymphovenous atresia.

OUTCOMES

Mortality from nonimmune hydrops remains high at approximately 50% despite recent advances in diagnosis and treatment. Predictors of survival include gestational age at birth and degree of illness at the time of birth. Infants with parvovirus, isolated neonatal chylothorax, and SVT have the highest survival.

Table 143.1 Principal Diagnoses Associated with Nonimmune Hydrops Fetalis

CARDIOVASCULAR (21%)
STRUCTURAL
- Hypoplasias (left or right heart)
- AV canal defect
- Single ventricle
- Transposition of great arteries
- Septal defects (VSD/ASD)
- Tetralogy of Fallot
- Ebstein anomaly
- Ductus arteriosus closure
- Truncus arteriosus
- Valvular (stenosis/insufficiency)

ARRYTHMIAS
- Atrial (flutter/tachyarrhythmia)
- Wolff-Parkinson-White
- Supraventricular tachycardia
- Long QT interval
- Heart block

CARDIOMYOPATHY
- Tumors
- Neoplasias
- Myopathies
- Cardiosplenic syndromes
- Hereditary cardiomyopathies

INFECTION (6.7%)
- Cytomegalovirus
- Parvovirus B19
- Syphilis
- Herpes simplex
- Rubella
- Coxsackievirus
- Leptospirosis
- *Trypanosoma cruzi*

INBORN STORAGE DISEASE (1.1%)
- Gaucher disease
- GM1 gangliosidosis
- Sialidosis
- MPS IVA and VII
- Mucolipidosis type I+II
- Galactosialidosis
- Niemann-Pick type C

TTTS-PLACENTAL (5.6%)
Twin
- TTTS
- Acardiac twin

Placental
- Umbilical vein thrombosis
- Umbilical cord angiomyxoma
- True cord knot
- Chorionic vein thrombosis
- Rare placenta disorders

THORACIC/EXTRATHORACIC MASS/LYMPHATIC (12.4%)
Mass Effect
- Diaphragmatic hernia
- Congenital pulmonary adenomatoid malformation
- Intrathoracic mass
- Pulmonary sequestration
- Chylothorax
- Airway obstruction
- Pulmonary lymphangiectasia
- Bronchogenic cyst

Other
- Milroy syndrome
- Generalized lymphatic dysplasia
- Lymphedema-distichiasis syndrome

Skeletal Dysplasias
- Thanatophoric dysplasia
- Short rib polydactyly
- Hypophosphatasia
- Osteogenesis imperfecta chondrogenesis
- Campomelic dysplasia
- Lethal achondroplasia
- Nager syndrome

IDIOPATHIC (17.8%)
CHROMOSOMAL (13.4%)
TRISOMY
- 21
- 18
- 13

MONOSOMY
- 45, X
- 45, X (mosaic)

DUPLICATIONS
- 18 q +
- 11p

DELETIONS
- 13 q −
- 17 q −

TRIPLOIDY

HEMATOLOGIC (10.4%)
- Alpha-thalassemia
- Hereditary stomatocytosis
- Fetomaternal hemorrhage
- Glucose-6-phosphate deficiency
- Leukemia
- Pyruvate kinase deficiency
- Red blood cell aplasias
- Diamond-Blackfan syndrome

GASTROINTESTINAL (0.5%)
- Duodenal atresia
- Duodenal diverticulum
- Jejunoileal atresia
- Volvulus
- Imperforate anus
- Meconium peritonitis
- Intestinal malrotation
- Intestinal duplication
- Hepatic fibrosis
- Cholestasis
- Biliary atresia
- Hepatic vascular malformations
- Hepatitis
- Hepatic necrosis
- Liver tumor or cysts

SYNDROMIC/MISCELLANEOUS (8.1%)
- Noonan syndrome and other RASopathies
- Arthrogryposis
- Multiple pterygium syndrome
- Neu-Laxova syndrome
- Pena-Shokeir syndrome
- Myotonic dystrophy
- Saldino-Noonan syndrome
- Francois syndrome, type III
- Familial nuchal bleb
- Elejalde syndrome
- Thoracoabdominal syndrome

URINARY TRACT MALFORMATION (2.3%)
- Urethral stenosis
- Urethral atresia
- Posterior urethral valve
- Finnish type nephrosis
- Edwards (prune belly) syndrome

OTHER
- HLH
- IPEX
- Nemaline myopathy
- Multiple pterygium syndrome
- Hyper IgE syndrome

ASD, Atrial septal defect; AV, arteriovenous; HLH, hemophagocytic lymphohistiocytosis; IPEX, immune dysregulation polyendocrinopathy enteropathy X-linked, MPS, mucopolysaccharide; TTTS, twin-twin transfusion syndrome; VSD, ventricular septal defect.
Modified from Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine Diseases of the Fetus and Infant*, 11th ed. Philadelphia: Elsevier; 2020: Table 23.4, p 381.

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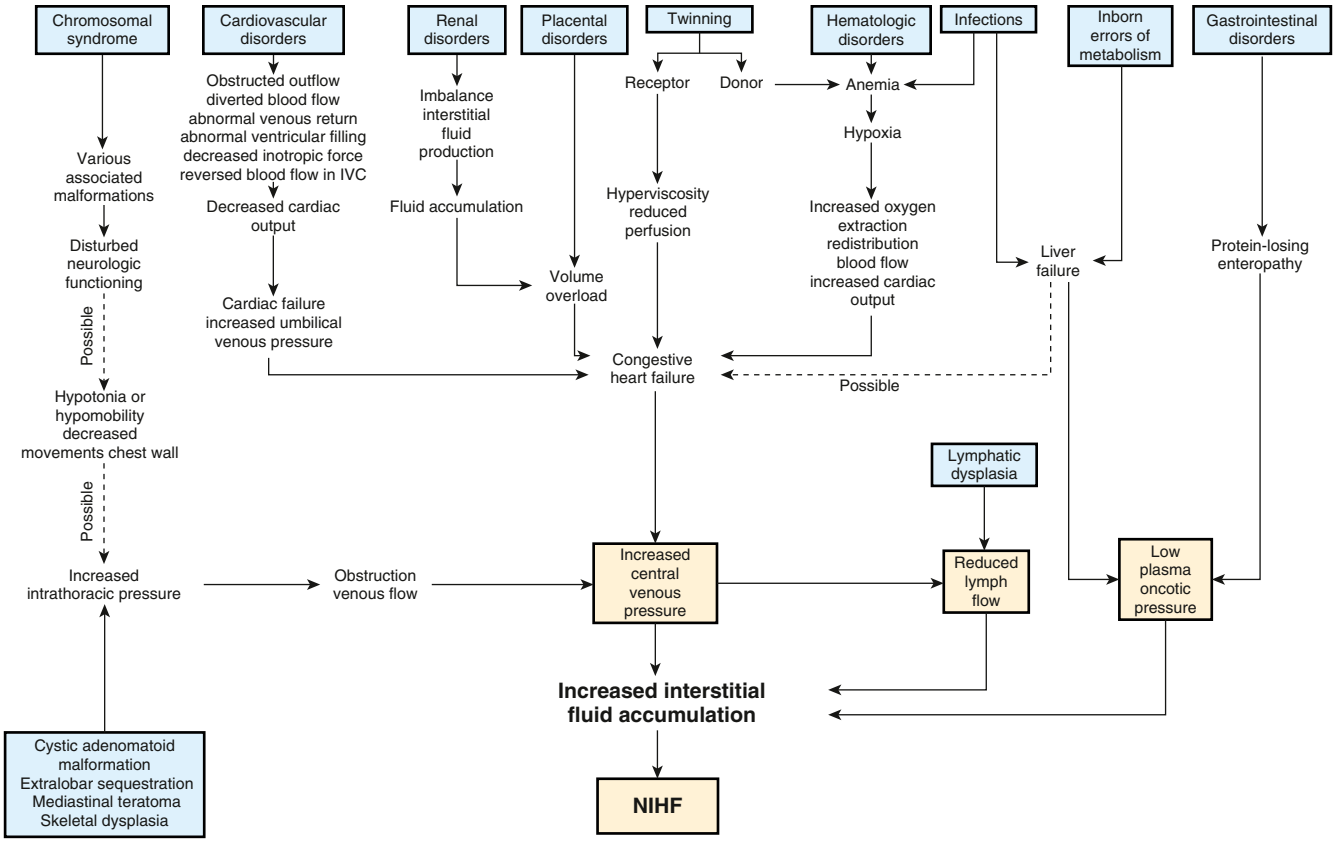

Fig. 143.2 Impact of various etiologies for nonimmune hydrops on fluid homeostasis. IVC, Inferior vena cava; NIHF, nonimmune hydrops fetalis. *(Adapted from Bellini C, Hennekam RCM. Non-immune hydrops fetalis: a short review of etiology and pathophysiology.* Am J Med Genet. *2012;158A:597–605.)*

Chapter 144

The Umbilicus

Eric C. Eichenwald

The umbilical cord typically consists of two umbilical arteries, the umbilical vein, and a gelatinous substance called Wharton jelly, all contained within a sheath derived from the amnion and coiled into a helical shape. The muscular umbilical arteries carry deoxygenated blood from the fetus to the placenta and are contiguous with the fetal internal iliac arteries. The umbilical vein carries oxygenated blood from the placenta back to the fetus, where it flows into the inferior vena cava by way of the ductus venosus. The placenta contains an estimated 20 mL/kg of blood; current recommendations are to delay clamping of the cord at delivery for 30-60 seconds in both term and preterm infants, to facilitate placental transfusion. At term, a normal umbilical cord is approximately 55 cm long. Abnormally short cords are associated with conditions causing decreased fetal movement, including fetal hypotonia, oligohydramnios, and uterine constraint, and lead to increased risk for complications during labor and delivery for both mother and infant. Long cords (>70 cm) increase the risk for true knots, wrapping around the fetus, and/or prolapse. Straight uncoiled cords are associated with anomalies, fetal distress, and intrauterine fetal demise.

When the cord is cut after birth, portions of these structures remain in the base but gradually become obliterated. The blood vessels are functionally closed but anatomically patent for 10-20 days. The umbilical arteries become the lateral umbilical ligaments; the umbilical vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. The umbilical cord stump usually sloughs within 2 weeks. Delayed separation of the cord, after more than 1 month, has been associated with neutrophil chemotactic defects and overwhelming bacterial infection (see Chapter 168).

A single umbilical artery is present in approximately 5-10/1,000 births; the frequency is higher (35-70/1,000) in twin births. It is estimated that 20–30% of infants with a single umbilical artery have other (and often multiple) congenital structural abnormalities. The presence of multiple anomalies is suggestive of an abnormal karyotype, including trisomies. Infants with an isolated single umbilical artery are not thought to be at increased risk of having a chromosomal anomaly, and no specific evaluation is indicated for these infants aside from a thorough physical examination.

The **omphalomesenteric duct (OMD)** is an embryonic connection between the developing midgut and the primitive yolk sac. It typically involutes at 8-9 weeks' gestation, but failure of this process can leave an abnormal connection between the umbilical cord and the gastrointestinal (GI) tract. The most common remnant of the OMD is a **Meckel diverticulum** (see Chapter 377), whereas abnormalities that would become symptomatic in the neonatal period include a **sinus** or **fistula** that would drain mucus or intestinal contents through the umbilicus. An umbilical **polyp** is one of the least common OMD remnants and represents exposed GI mucosa at the umbilical stump. The tissue of the polyp is bright red, firm, and has a mucoid secretion. Therapy for all OMD remnants is surgical excision of the anomaly.

A **persistent urachus** (urachal cyst, sinus, patent urachus, or diverticulum) is a result of failure of closure of the allantoic duct and may be associated with bladder outlet obstruction. Patency should be suspected if a clear, light-yellow, urine-like fluid is being discharged from the umbilicus. Symptoms include drainage, a mass or cyst, abdominal pain, local erythema, and infection. Urachal anomalies should be investigated by ultrasonography and a cystogram. Therapy for a persistent urachus is surgical excision of the anomaly and correction of any bladder outlet obstruction if present.

UMBILICAL HEMORRHAGE

Hemorrhage from the umbilical cord may be the result of trauma, inadequate ligation of the cord, or failure of normal thrombus formation. It may also indicate hemorrhagic disease of the newborn or other coagulopathies (especially factor XIII deficiency), septicemia, or local infection. The infant should be observed frequently during the first few days of life so that if hemorrhage does occur, it will be detected promptly.

UMBILICAL GRANULOMA

The umbilical cord stump usually dries and separates within 1-2 weeks after birth. The raw surface becomes covered by a thin layer of skin; scar tissue forms, and the wound is usually healed within 12-15 days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection or incomplete epithelialization may result in a moist, granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

Persistence of granulation tissue at the base of the umbilicus is common. The tissue is soft, 3-10 mm in size, vascular and granular, colored dull red or pink, and may have a seropurulent discharge. Granulation tissue is treated by cauterization with silver nitrate, repeated at intervals of several days until the base is dry.

UMBILICAL INFECTIONS

The devitalized umbilical cord provides an ideal medium for bacterial growth and a potential portal of entry for microbes. The term **omphalitis** refers to infection of the umbilical cord stump, navel, or the surrounding abdominal wall. Omphalitis must be distinguished from local irritation from the umbilical cord clamp. Erythema that extends to the abdominal wall, particularly tracking superiorly is concerning. Most term infants with mild localized omphalitis appear well and are afebrile. However, ~10–15% are acutely ill and at risk for bacteremia, spreading cellulitis, necrotizing fasciitis, and extension into the portal vein and liver. **Necrotizing fasciitis** (which is often polymicrobial) is associated with a high mortality rate and is often associated wth neutropenia. Treatment of omphalitis includes prompt antibiotic therapy with agents effective against *Staphylococcus aureus* and *Escherichia coli*, such as an antistaphylococcal penicillin or vancomycin in combination with an aminoglycoside. If abscess formation or necrotizing fasciitis has occurred, surgical consultation for incision and drainage or debridement may be required.

In community and primary care settings in developing countries, topical application of chlorhexidine to the umbilical cord has been shown to reduce omphalitis and neonatal mortality. In hospital settings in developed countries, there is no convincing evidence that application of antiseptics (including triple dye, alcohol, or chlorhexidine) is superior to *dry cord care* in minimizing the risk of omphalitis for infants in these settings, although these treatments do reduce bacterial colonization.

UMBILICAL HERNIA

Often associated with **diastasis recti**, an umbilical hernia is caused by incomplete closure or weakness of the muscular umbilical ring. Predisposing factors include Black race and low birthweight. The hernia appears as a soft swelling covered by skin that protrudes during crying, coughing, or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from <1 cm in diameter to as much as 5 cm (2 inches), but larger defects are rare. Most umbilical hernias that appear before age 6 months disappear spontaneously by 1 year. Even large hernias (5-6 cm in all dimensions) have been known to disappear spontaneously by 5-6 years. Strangulation of intestinal contents is *extremely rare*. Surgery is not advised unless the hernia persists to age 4-5 years, causes symptoms, becomes strangulated, or becomes progressively larger after age 1-2 years. Defects exceeding 2 cm are less likely to close spontaneously.

CONGENITAL OMPHALOCELE

An **omphalocele** is a herniation or protrusion of the abdominal contents into the base of the umbilical cord (Fig. 144.1). In contrast to the more common umbilical hernia, the sac is covered with peritoneum without overlying skin, and the insertion of the distal umbilical cord into the sac itself distinguishes this condition from other abdominal wall defects such as gastroschisis. The size of the sac that lies outside the abdominal cavity depends on its contents. Herniation of intestines into the cord occurs in approximately 1/5,000 births, and herniation of liver and intestines in 1/10,000 births. The abdominal cavity may be proportionately small because of the lack of space-occupying viscera. Treatment for an omphalocele consists of covering the sac with moist, sterile dressings, then initiating prompt surgical repair if the abdomen is able to accommodate the eviscerated organs. If the omphalocele is too large to allow immediate repair, continued dressings may temporize and encourage epithelialization of the sac. Occasionally, mesh or similar synthetic material may be used to cover the viscera if the sac has ruptured or if excessive mobilization of the tissues would be necessary to cover the mass and its intact sac.

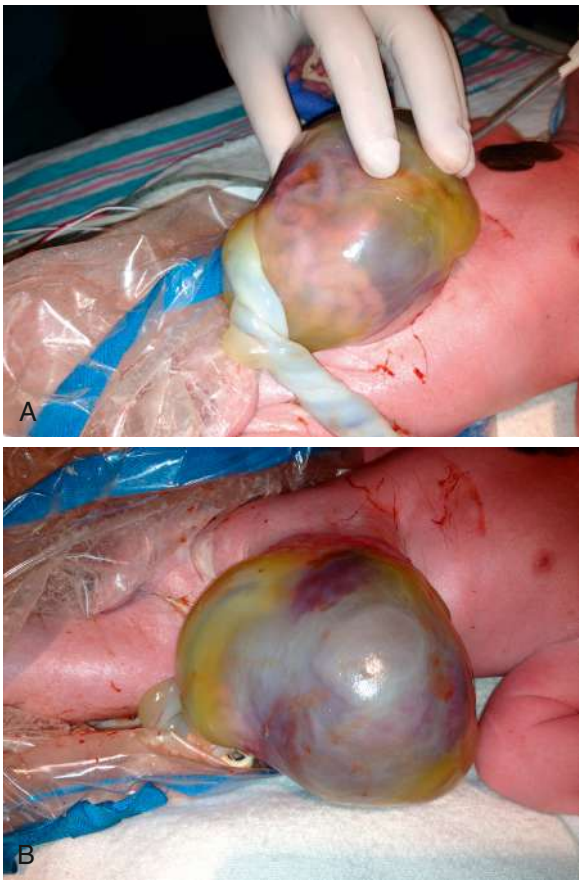

Fig. 144.1 A, Omphalocele with umbilical cord insertion into the sac and intestine visible. B, Omphalocele with sac containing liver. (*Courtesy Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.*)

Many infants with omphalocele (50–70%) have associated malformations, and about 30% have chromosomal abnormalities. The likelihood of an abnormal karyotype is increased when the liver is *intracorporeal* (not within the sac). Omphalocele can be part of well-defined syndromes, including **Beckwith-Wiedemann syndrome**, characterized by omphalocele, macrosomia, and hypoglycemia. The survival rate for affected infants is largely determined by the presence of associated malformations or chromosomal abnormalities. For patients with isolated omphalocele, the survival rate is >90%.

UMBILICAL TUMORS

Tumors of the umbilicus are rare and include angioma, enteroteratoma, dermoid cyst, myxosarcoma, and cysts of urachal or OMD remnants.

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Chapter 145

Neonatal Abstinence Syndrome

Stephen W. Patrick

Neonatal abstinence syndrome (NAS) is a drug withdrawal syndrome that occurs among some substance-exposed infants shortly after birth. The syndrome most commonly occurs after in utero exposure to opioids and is also called neonatal opioid withdrawal syndrome (NOWS). Between 2000 and 2017, the rate of NAS in the United States increased sixfold reaching 7.2 per 1,000 hospital births, which mirrors the rise of other population-wide opioid-related complications including overdose deaths. The opioid overdose crisis in the United States was first driven by prescription opioids (e.g., oxycontin), then heroin, and more currently by illicitly produced fentanyl. For pregnant women opioid use disorder (OUD), or continued use of an opioid despite adverse consequences, often begins before pregnancy and is associated with myriad social risks including trauma and physical abuse. Treatment of OUD, especially with medications for OUD (MOUD), is effective in improving pregnancy outcomes. MOUD, including buprenorphine and methadone, has been shown to reduce risk of relapse, overdose death, HIV and hepatitis C virus (HCV), and preterm birth. **Methadone** is a full μ-opioid agonist, generally given once daily, and is administered through highly regulated opioid treatment programs. **Buprenorphine** is a partial μ-opioid agonist and a partial k-antagonist, can be prescribed in the outpatient setting, and is more widely available. Accessing treatment can be challenging for pregnant women, with studies showing they are nearly 20% less likely to be accepted for treatment than nonpregnant women. Notably, MOUD such as methadone and buprenorphine can cause NAS; however, this is generally thought of as a preferable outcome when compared to preterm birth or overdose.

The clinical signs of NAS are generally associated with neurologic (e.g., tremor), gastrointestinal (e.g., poor feeding), and autonomic signs (e.g., tachypnea) and can be documented using the NAS score (Fig. 145.1) as well as the Eat, Sleep, Console (ESC) assessment tool (Table 145.1).

NEONATAL ABSTINENCE SCORE

Date: _____ Weight: _____

System	Signs & Symptoms	Score	Time AM / PM	Comments
Central Nervous System Disturbances	Excessive High Pitched Cry	2		
	Continuous High Pitched Cry	3		
	Sleeps < 1 Hour After Feeding	3		
	Sleeps < 2 Hours After Feeding	2		
	Sleeps < 3 Hours After Feeding	1		
	Hyperactive Moro Reflex	2		
	Markedly Hyperactive Moro Reflex	3		
	Mild Tremors Disturbed	1		
	Moderate - Severe Tremors Disturbed	2		
	Mild Tremors Undisturbed	3		
	Moderate - Severe Tremors Undisturbed	4		
	Increased Muscle Tone	2		
	Excoriation (Specific Area)	1		
	Myoclonic Jerks	3		
	Generalized Convulsions	5		
Metabolic / Vasomotor / Respiratory Disturbances	Sweating	1		
	Fever < 101° F (37.2° - 38.2° C)	1		
	Fever ≥ 101.1° F (≥38.4° C)	2		
	Frequent Yawning (> 3 - 4 Times/Interval)	1		
	Mottling	1		
	Nasal Stuffiness	1		
	Sneezing (> 3 - 4 Times/Interval)	1		
	Nasal Flaring	2		
	Respiratory Rate - 60/min	1		
	Respiratory Rate - 60/min with Retractions	2		
Gastrointestinal Disturbances	Excessive Sucking	1		
	Poor Feeding	2		
	Regurgitation	2		
	Projectile Vomiting	3		
	Loose Stools	2		
	Watery Stools	3		
	TOTAL SCORE			
	Initials of Scorer			

Fig. 145.1 Data from Amin A, Frazie M, Thompson S, Patel A. Assessing the Eat, Sleep, Console model for neonatal abstinence syndrome management at a regional referral center. *J Perinatol*. 2023 Apr 25:1–7; Blount T, Painter A, Freeman E, et al. Reduction in length of stay and morphine use for NAS with the "Eat, Sleep, Console" Method. *Hosp Pediatr*. 2019;9:615–623; Glait M, Moyer A, Saudek K, et al. Addressing drivers of healthcare utilization for neonatal opioid withdrawal syndrome. *J Perinatol*. 2023;43):392–401; Grossman M. Eat, Sleep, Console (ECS) care tool. 2017 ESC 3rd ed. 1.30.20; Young LW, Ounpraseuth ST, Merhar SL, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. 2023;388:2326–2336.)

Table 145.1 Eat, Sleep, Console (ESC) Assessment Approach to Neonatal Opioid Withdrawl

EATS
Takes > 10 min to coordinate feeding with hunger cues
< 10 min for breastfeeds
< 10 mL of a feed

SLEEPS
< 1 hr after a feed

CONSOLES
Takes > 10 min to be consoled
Cannot stay consoled for 10 min

Nonpharmacologic interventions include rooming in, caregiver presence, skin to skin contact, holding/cuddling, safe swaddling (avoid face), feed on demand after hunger cues, breastfeeding, non-nutritive sucking, quiet low stimulation low-light environment, rhythmic motion, additional caregiver support, minimal disruptions in environment, cluster care to awake times, safe sleep, caregiver self-care and rest.

These parameters suggest withdrawl.
Data from Amin A, Frazie M, Thompson S, Patel A. Assessing the Eat, Sleep, Console model for neonatal abstinence syndrome management at a regional referral center. *J Perinatol*. 2023 Apr 25:1–7; Blount T, Painter A, Freeman E, et al. Reduction in length of stay and morphine use for NAS with the "Eat, Sleep, Console" Method. *Hosp Pediatr*. 2019;9:615–623; Glait M, Moyer A, Saudek K, et al. Addressing drivers of healthcare utilization for neonatal opioid withdrawal syndrome. *J Perinatol*. 2023;43):392–401; Grossman M. Eat, Sleep, Console (ECS) care tool. 2017 ESC 3rd ed. 1.30.20; Young LW, Ounpraseuth ST, Merhar SL, et al. Eat, sleep, console approach or usual care for neonatal opioid withdrawal. *N Engl J Med*. 2023;388:2326–2336.

The timing of NAS onset can be related to several factors, including the last maternal use and half-life of the opioid. NAS signs can rarely begin within 24 hours of birth but more commonly occur within 48 hours after short-acting opioids, and 72-96 hours after exposure to long-acting or maintenance opioids (e.g., methadone). For these reasons, it is recommended to observe opioid-exposed infants for at least 3 days after birth for an infant exposed to short-acting opioids and 5 days for longer half-life opioids such as buprenorphine. Tremors, poor feeding, excessive crying, poor sleeping, and hyperirritability are the most prominent signs of NAS. Other signs include sneezing, yawning, hiccups, myoclonic jerks, skin breakdown and abrasions, vomiting, loose stools, nasal stuffiness, and seizures. Many prenatal and postnatal factors can influence the severity and duration of withdrawal. Polysubstance use, particularly with cigarettes, gabapentin, benzodiazepines, and selective serotonin reuptake inhibitors, has been associated with a higher risk or more severe NAS, whereas breastfeeding after delivery, rooming-in, and standardizing care processes (i.e., following protocols) have been associated with lower risk or less severe NAS (see Table 145.1 for nonpharmacologic interventions).

Identifying substance use as early as possible in pregnancy is critical to improving pregnancy outcomes. For that reason, it is recommended to perform universal screening for substance use using a standardized and validated tool such as the four Ps:

- **Parents:** Did any of your parents have problems with alcohol or other drug use?
- **Partner:** Does your partner have a problem with alcohol or drug use?
- **Past:** In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?
- **Present:** In the past month, have you drunk any alcohol or used other drugs?

Screening can be augmented with toxicology testing of the mother or infant; it is important to recognize that toxicology testing has limitations and for some substances may only capture a short window of exposure. Toxicology testing of pregnant women requires informed consent but is not needed for infants if done as part of routine care.

Testing urine of mothers or infants can capture recent exposures, whereas umbilical cord and meconium testing will capture a longer window of substance use. Toxicology testing may not be needed if women are in treatment and receive routine testing in pregnancy.

TREATMENT AND SETTING

Hospitals should have standardized protocols for the observation, scoring, and treatment of the opioid-exposed infant. The first line of treatment for all opioid-exposed infants is **nonpharmacologic support**, including rooming-in, breastfeeding, and tailoring the environment to not overstimulate the infant. Importantly, care for opioid-exposed infants and those diagnosed with NAS does not require admission to a neonatal intensive care unit (NICU); admission to a NICU may cause undue separation of the maternal–infant dyad as well as exacerbate clinical signs of withdrawal by placing the infant in a loud environment. Breastfeeding, in addition to its well-documented benefits, can also reduce NAS severity and can safely occur with maternal treatment using MOUD. Although there are no evidence-based guidelines, consensus guidelines suggest breastfeeding can be encouraged if there has been no relapse within 30 days of birth and should be encouraged if there has been no relapse within 90 days of birth. Untreated HIV is a contraindication to breastfeeding; however, breastfeeding is safe with HCV unless there are cracked or bleeding nipples.

The decision for pharmacologic treatment has been traditionally based on the nursing scoring assessment tool, and the most widely used tool is a modification of the Finnegan scoring tool (see Fig. 145.1). Other scoring tools include the Neonatal Narcotic Withdrawal Index, Neonatal Withdrawal Inventory, and MOTHER NAS Scale.

The **ESC model** is very useful and is an evidenced-based approach for improved outcomes and fewer pharmacologic interventions (Table 145.1). An inability to eat, sleep, or be consoled in at least two of the three parameters in the presence of nonpharmacologic interventions warrants pharmacologic therapy, usually with oral liquid morphine plus continued nonpharmacologic interventions. Other etiologies of poor eating, sleeping, and consolability must be evaluated. The main objectives when initiating pharmacologic treatment is to control clinical signs of withdrawal and to prevent adverse events (e.g., seizure). Excessive weight loss may be an indication for pharmacotherapy regardless of other clinical signs.

Pharmacologic treatment for NAS, when necessary, should be done with an opioid, and the most commonly used are morphine or methadone (Table 145.2). **Morphine** is a short-acting opioid given every 3 hours as a weight-based or clinical sign-based regimen. **Methadone** is a long-acting opioid that can generally be given twice a day after loading doses. **Buprenorphine** is an effective agent that may be superior to morphine; its use may be associated with a short duration of treatment and length of stay, as well as few adverse effects and less use of additional medications. Clinical trials have shown methadone and buprenorphine to decrease length of treatment when compared with morphine. Buprenorphine and some methadone formulations contain high ethanol levels, which may be deleterious to the infant and should be avoided. Closely adhering to NAS treatment protocols with guidelines on initiation and weaning have been shown to decrease both length of treatment and length of stay.

Adjuvant therapy is generally initiated in the unusual situation when the primary opioid is not effective in controlling the signs of NAS. The two medications used as adjuvant therapy are **phenobarbital** and **clonidine**. American Academy of Pediatrics (AAP) guidelines suggest clonidine be used as adjuvant therapy; phenobarbital should be avoided if possible as some studies suggest long-term use can be associated with developmental delay.

Long-term studies of opioid-exposed infants are lacking, and many are confounded by co-exposures (e.g., alcohol), maternal health (e.g., poor nutrition), or social risk (e.g., trauma), all of which could influence developmental outcomes. Still, infants should be closely monitored to optimize developmental trajectory. In many states a diagnosis of NAS qualifies for early intervention services, which are part of the Individuals with Disability and Education Act Part C, and infants should be referred to this service. Other supportive referrals should be

Table 145.2 Medications Used in Pharmacologic Treatment of Neonatal Abstinence Syndrome

DRUG	INITIAL DOSING	DOSING INCREASES	WEANING SCHEDULE	ADD ADJUVANT THERAPY
Morphine	0.05 mg/kg/dose q3h	Increase dose 10–20%	10% of stabilizing dose q24h	>1 mg/kg/day of morphine Unable to wean for 2 days
Methadone	0.1 mg/kg/dose q6h for 4 doses	Increase to q4h if unable to capture	0.7 mg/kg/dose q12h × 2 doses, then 0.05 mg/kg/dose q12h × 2 0.04 mg/kg/dose q12h × 2 0.03 mg/kg/dose q12h × 2 0.02 mg/kg/dose q12h × 2 0.01 mg/kg/dose q12h × 2 0.01 mg/kg/dose q24h × 1	Unable to wean for 2 days
Buprenorphine	4 µg/kg q8h	2 µg/kg until maximum of 15 µg/kg	3 µg/kg/dose q8h × 3 doses 2 µg/kg/dose q8h × 3 2 µg/kg/dose q8h × 2 2 µg/kg/dose q24h × 1	Unable to wean for 2 days
Phenobarbital	20 mg/kg	—	5 mg/kg daily	N/A
Clonidine	1.5 µg/kg/dose q3h	25% dose escalation q24h	10% every day	N/A

N/A, Not available; q24h, every 24 hours.

considered, including home visitation programs and Early Head Start. Further, in the discharge process clinicians should also assess other risk, including HIV and HCV exposure, which must be followed in the outpatient setting. Hospitals should standardize the discharge process for opioid-exposed infants to ensure connection to postdischarge services.

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Chapter 146

Fetal Alcohol Spectrum Disorder

Susan A. Friedman and Hallam Hurt

Alcohol is a known teratogen that can cause irreversible central nervous system (CNS) damage. Injury can include reduced brain volume, particularly for the frontal lobe, and thinning of the corpus callosum. These injuries can lead to CNS dysfunction that can range from relatively mild to severe. Prenatal alcohol exposure (PAE) affects all stages of brain development from neurogenesis to myelination, through mechanisms that include disrupted cell-cell interactions, altered gene expression, and oxidative stress leading to abnormalities such as reduced brain volume in the frontal lobe, striatum and caudate nucleus, thalamus, and cerebellum; thinning of the corpus callosum; and abnormal functioning of the amygdala.

PAE can result in a spectrum of outcomes. The term fetal alcohol spectrum disorder (FASD) is the umbrella term that encompasses a group of conditions associated with PAE. The FASD group of disorders includes fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental disorder (ARND), alcohol-related birth defect (ARBD), and neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE).

EPIDEMIOLOGY

According to the CDC, approximately 1 in 7 pregnant women report consuming alcohol within the past 30 days. Approximately 20-30% report drinking at some point during the pregnancy, and more than 5% report binge drinking. consuming alcohol within the last 30 days, with ~20% reporting binge drinking. Because almost 50% of pregnancies in the United States are unplanned, unintentional PAE can occur before a woman knows she is pregnant.

PREVALENCE

FASDs are the most common causes of preventable developmental delay and intellectual disability. Prevalence rates vary across reports. The US Centers for Disease Control and Prevention (CDC) FAS Surveillance Network reported prevalence rate across several populations of 0.3 out of 1,000 children from 7 to 9 years of age. This prevalence rate is much lower than that obtained by active case ascertainment studies in the United States and Western Europe, which have estimated prevalence rates of 2–5%. Another study reported similar rates, 24-48 cases per 1,000 children (2.4–4.8%) for all FASDs, and 6-9 cases per 1,000 (0.6–0.9%) for FAS specifically. Studies that have examined PAE by anonymous meconium testing demonstrate 4.26 times greater identification of alcohol use during pregnancy compared with maternal self-report. Rates of FASDs have been reported to be higher in children living in poverty, in Indigenous populations, and in children living in foster care. The rate of FASDs for children in foster care has been found to be 10 to 15 times higher than that for children in the general population. FASDs often go undetected in these children, and as many as 86.5% of foster and adopted youth with FASDs go undiagnosed or are diagnosed incorrectly within the FASD spectrum. Children adopted internationally represent another high-risk group, particularly those adopted from Eastern Europe. Children adopted from orphanages and other children with a history of early trauma, such as those in foster care, may also exhibit symptoms of posttraumatic stress disorder (PTSD) and other neurobehavioral and developmental issues that can overlap with those of FASD, including those without physical features (ARND or ND-PAE). The impairments seen in children with an FASD may also include the negative impact of additional prenatal and postnatal risk factors.

DIAGNOSTIC SYSTEMS

The most widely used diagnostic guidelines are the Hoyme FASD diagnostic guidelines (revised 2016), the University of Washington 4-Digit Diagnostic Code (2004), the CDCFAS guidelines (revised

2004, only includes FAS), and the Canadian FASD guidelines (revised 2016).

These FASD diagnostic guidelines overlap but also have important distinctions. The Hoyme system uses more stringent alcohol exposure criteria than the 4-Digit Diagnostic Code. Both the Hoyme system (2016), and the 4-Digit Diagnostic Code system use the three diagnostic criteria of facial findings, growth restriction, and CNS abnormalities and both include a spectrum of disorders under the umbrella term of *fetal alcohol spectrum disorder* (FASD). However, they do differ in diagnostic tools, specific criteria used to define each category, and in diagnostic nomenclature. The result of these differences and others is that there may not be total agreement between the two in the diagnosis of a given patient. The CDC guidelines establish criteria only for FAS and require the three diagnostic criteria of facial findings, growth restriction, and CNS abnormalities, with or without documented PAE. In the updated Canadian guidelines, "fetal alcohol spectrum disorder" is considered a diagnostic term with two categories: FASD with sentinel facial features and FASD without sentinel facial features. These guidelines eliminate growth restriction as a required diagnostic criterion. They include an at-risk category for children with confirmed PAE who were too young to meet the criteria for neurodevelopmental deficits, or in whom assessment was incomplete. They also include a category for children with cardinal facial features without documentation or evidence of severe impairment in neurodevelopmental domains. There is no universal acceptance of one system. If less stringent criteria are used, the sensitivity increases, which may lead to overdiagnosis. Additional expert evaluation is then needed to confirm a diagnosis. In contrast, using more stringent criteria leads to greater specificity but may underdiagnose FASD.

Historical and Clinical Features

The historical and clinical features shared by all previously described diagnostic systems (although not required by all of the disorders) include five categories: (1) PAE, (2) three key facial features, (3) prenatal/postnatal growth restriction, (4) deficient brain growth and/or significant structural brain abnormalities, and (5) neurobehavioral impairment.

Prenatal Alcohol Exposure

A safe threshold or pattern of alcohol consumption during pregnancy has not been identified, and any PAE at any stage of gestation is believed to present a risk to a developing fetus. Significant alcohol exposure has been carefully defined in the 2016 updated Hoyme guidelines as follows.

One or more of the following exposures, beginning 3 months before pregnancy and continuing until delivery, with a standard drink defined as 1.5 oz of hard liquor, 5 oz of wine, or 12 oz of beer or wine cooler:

- ≥6 drinks/week for ≥2 weeks during pregnancy
- ≥3 drinks per occasion on ≥2 occasions
- Documented alcohol-related social or legal problems before or during pregnancy or a history of treatment for an alcohol-related condition
- Documentation of intoxication of blood, breath, or urine alcohol testing
- Positive testing with an established biomarker of alcohol exposure during pregnancy or at birth
- Positive finding on a validated screening tool for drinking during pregnancy

Information can be obtained from a variety of sources in addition to the birth mother, including family members, foster or adoptive parents, social service agencies who observed maternal alcohol consumption during pregnancy, or medical records that document PAE, alcohol treatment, or social, legal, or medical problems related to drinking during pregnancy. Binge drinking (4 or more drinks per occasion) has been shown to be the most harmful to fetal development. PAE in the first trimester leads to the classic facial dysmorphia associated with FAS and other structural defects. PAE can have other deleterious effects (e.g., spontaneous abortion, growth defect, CNS effects) on the fetus throughout the pregnancy.

Several well-validated screens are used to identify alcohol use in pregnant and nonpregnant women of childbearing years, including the assessments of Tolerance, Annoyance, Cut Down, Eye-Opener (T-ACE), Cut Back, Annoyed, Guilty, Eye-Opener (CAGE); Car; Relax; Alone; Forget; Friends; Trouble (CRAFFT); Alcohol Use Disorders Identification Test (Audit-C); and Tolerance, Worried, Eye-Opener, Amnesia, Kut Down (TWEAK). There are, however, no well-validated screens designed to ask about past consumption of alcohol. Pediatricians can ask the following two questions to determine the likelihood of significant PAE: "In the 3 months before you knew you were pregnant, how many times did you have 4 or more alcohol drinks in a day?" and "During your pregnancy, how many times did you have any alcohol?" If a positive response is given to either question, the clinician can follow up to determine the level of PAE by asking the following: (1) "During your pregnancy, on average, how many days per week did you have any alcohol?"; (2) "During your pregnancy, on a typical day when you had an alcoholic beverage, how many drinks did you have?"; and (3) "During your pregnancy, what was the maximum number of drinks that you had in a day?"

Dysmorphologic Facial Features

The three key, facial dysmorphologic features include short palpebral fissures, a thin vermilion border of the upper lip, and a smooth philtrum (Fig. 146.1). Measurement of the **palpebral fissure length (PFL)** is shown in Figure 146.2. There are several different PFL charts that can be used to plot this measurement. That of Hall is included here (Fig. 146.3), with additional charts listed under Additional Resources for Healthcare Providers. In addition, different diagnostic systems have different cutoffs to define the criteria. Evaluation of the philtrum and upper lip utilizes the Lip-Philtrum

Fig. 146.1 Examples of facial features of FAS in children of different ethnicities. **A**, White. **B**, Native American. **C**, Black. **D**, Asian. (*Copyright 2021 Susan (Astley) Hemingway PhD, University of Washington.*)

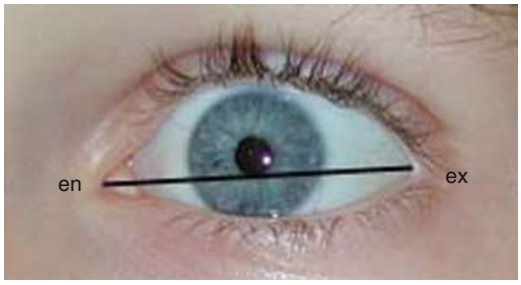

Fig. 146.2 The palpebral fissure length is defined by the distance between the endocanthion *(en)* and exocanthion *(ex)* landmarks. (*Copyright 2021 Susan (Astley) Hemingway PhD, University of Washington.*)

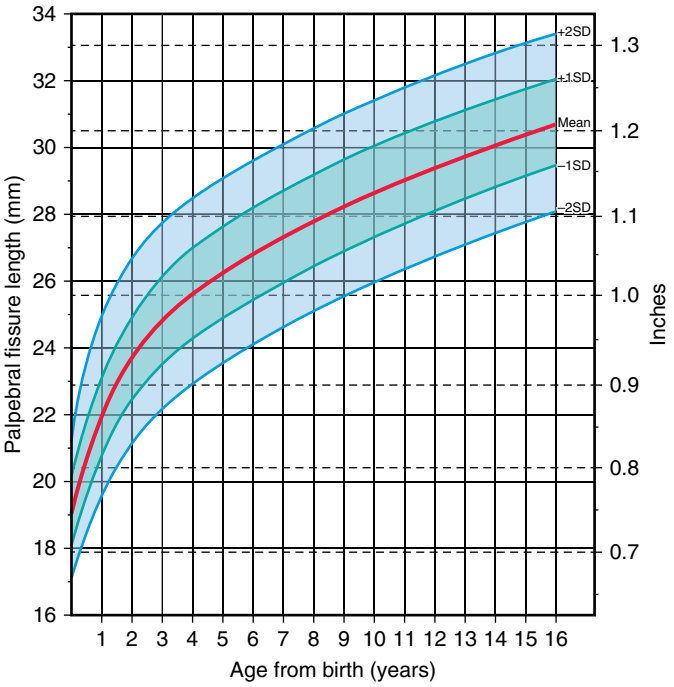

Fig. 146.3 Palpebral fissure measurements. (*From Hall JG, Froster-Iskenius UG, Allanson J, eds. Handbook of Normal Physical Measurements. Oxford: Oxford University Press; 1989: p. 150.*)

Guide developed at the University of Washington (Fig. 146.4), which can be obtained on request in digital format or as a laminated card from the University of Washington. Although this guide includes norms for White and Black children, additional work is needed on establishing norms for the three facial features across a wider range of racial groups.

Additional minor anomalies may also occur in association with PAE but are not included in the diagnostic criteria: mid-face hypoplasia, epicanthal folds, ptosis, strabismus, altered palmar crease ("hockey stick" and clinodactyly of the fifth finger [Fig. 146.5], "railroad track ears" [Fig. 146.6], hypoplastic nails, limited elbow supination, camptodactyly, hypertrichosis).

Prenatal/Postnatal Growth Deficiency

This is defined as ≤10th percentile for age (Hoyme and CDC) or ≤3rd percentile (4-Digit Diagnostic Code) for *either* height or weight. The systems also vary in the timing of the growth problems (prenatal/at birth, or at any point in life).

Deficient Brain Growth and Significant Structural Brain Abnormalities

Deficient brain growth is defined as an occipitofrontal head circumference (OFC) <10% for age, abnormal morphogenesis, or abnormal neurophysiology. The criteria additionally state that if the child has weight and height <10th percentile, then the OFC should be at or below the 3rd percentile. Structural brain abnormalities seen on brain imaging may include abnormalities of the corpus callosum, the cerebellum, or basal ganglia.

Neurobehavioral/Neurodevelopmental Impairment

These criteria can include abnormal findings on neurologic exam or seizures, and/or functional neurobehavioral or neurodevelopmental abnormalities. There is tremendous variability in the presentation of the neurobehavioral and neurocognitive features of children with FASD due to the timing and amount of PAE and unique characteristics of the birth mother and the child. The assessment of neurobehavioral impairment is also different for children under 3 years of age than for children 3 years or older.

The degree of developmental impairment can range from relatively mild delays to severe intellectual disability, although approximately 75% of individuals with an FASD *do not* have intellectual disability. In *infants*, the symptoms can be nonspecific and may include irritability, poor feeding, sleep difficulties, a tendency to become easily overstimulated, or difficulty forming attachments with caregivers. *Young children* may demonstrate developmental delays, inattention, impulsivity, internalizing and externalizing problems, social impairments and difficulty with peers, and behavioral difficulties such as mood lability, frequent tantrums, or aggression. The neurocognitive profile of children with an FASD that emerges at *elementary or middle school age* includes challenges with processing speed, memory, visual-spatial reasoning, math, auditory comprehension, use of pragmatic language, and executive functioning skills. In *adolescents*, difficulties with abstract reasoning, time and money management, and social and adaptive skills may become more pronounced.

The most common comorbid mental health condition seen in children with an FASD is attention-deficit/hyperactivity disorder (ADHD; see Chapter 50), which occurs in >50% of children. Individuals with FASD may also present with problems of self-regulation, impulse control, and adaptive functioning. Additional mental health disorders typically seen in children and adolescents include oppositional defiant and conduct disorder, anxiety disorder, adjustment disorder, sleep disorder, mood disorders (e.g., depression, bipolar disorder), and disinhibited social engagement disorder. FASD may increase the severity or complexity of these conditions.

DIAGNOSTIC CRITERIA

Five diagnoses included under the FASD umbrella include the following:

1. Fetal alcohol syndrome (FAS)
2. Partial fetal alcohol syndrome (pFAS)
3. Alcohol related neurodevelopmental disorder (ARND)
4. Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)
5. Alcohol related birth defects (ARBD)

The previously described clinical features with or without a history PAE are used to define the disorders within the FASD spectrum (Tables 146.1-146.5). As noted earlier, the criteria do vary somewhat depending upon which diagnostic system is used.

DIFFERENTIAL DIAGNOSIS

It is important to consider other causes of the facial features of FAS and pFAS, as each of these can be seen in certain genetic and teratogenic exposure conditions. Genetic conditions can include Williams syndrome, Dubowitz syndrome, Noonan syndrome, 22q11.2 deletion (velocardiofacial syndrome), Cornelia de Lange syndrome, chromosome 15q duplication syndrome, and others. Teratogenic exposure conditions include fetal valproate syndrome, fetal hydantoin syndrome, maternal phenylketonuria

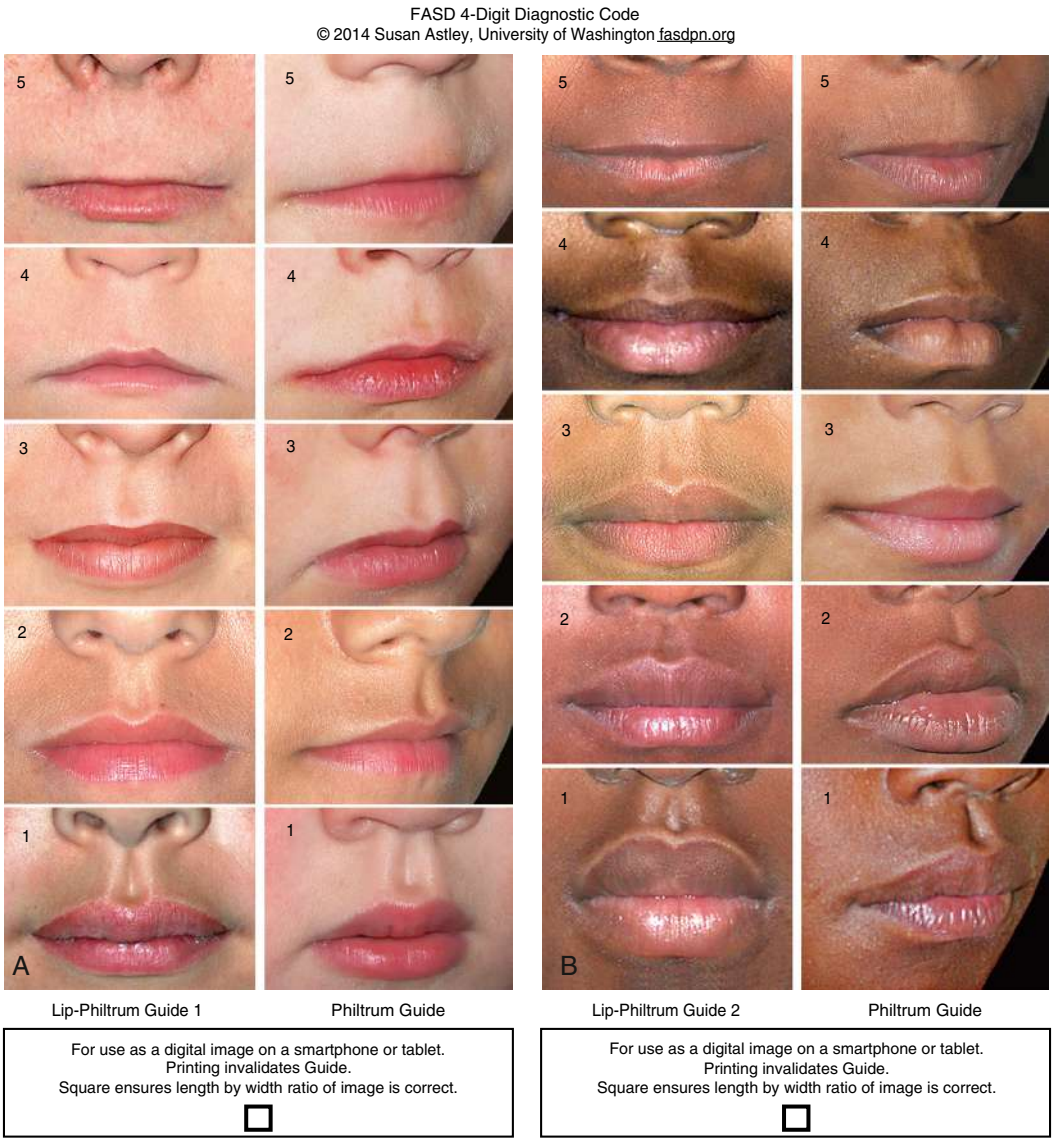

Fig. 146.4 University of Washington Lip-Philtrum Guides 1 (A) and 2 (B) are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip thickness and philtrum depth with Rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterize the FAS facial phenotype. Guide 1 is used for Whites and all other races with lips like Whites. Guide 2 is used for Blacks and all other races with lips like Blacks. Free digital images of these guides for use on smartphones are available from astley@uw.edu. (*Copyright 2021 Susan (Astley) Hemingway PhD, University of Washington.*)

(PKU) effects, toluene embryopathy, and others. Therefore a genetics evaluation may be warranted, especially when there is unconfirmed PAE.

The neurobehavioral issues associated with FASD can be difficult to distinguish from those of other behavioral health disorders, such as autism spectrum disorder, ADHD, intellectual disability, reactive attachment disorder, PTSD, exposure to other maternal substance use during pregnancy, and others. This is particularly the case when the FASD facial features are not present. Children who experience "adverse childhood experiences" (ACEs), such as neglect, abuse, poverty, and parental substance abuse, can have similar findings of hyperactivity, poor impulse control, emotional dysregulation, deficits in executive function, and memory weaknesses as children with FASD. Furthermore, these disorders are not mutually exclusive and more than one underlying disorder can result in the neurobehavioral issues found.

OUTCOMES

Children with an FASD are at higher risk for victimization and bullying, often due to poor social judgment. Children and adolescents who are not identified early and treated aggressively are significantly more likely to have secondary disabilities, including encounters with juvenile justice and incarceration, substance abuse problems, severe mental health problems, sexual promiscuity and other inappropriate sexual behaviors, high rates of school failure, dropout and under- or unemployment, health problems, and premature death. Children and adolescents with an FASD have a 95% lifetime likelihood of having a mental health diagnosis and are at higher risk for suicide. Although an FASD cannot be cured, the long-term negative effects of the brain injury caused by PAE can be reduced through aggressive, sustained intervention initiated early. Factors associated with a better outcome include early diagnosis (under age 6 years), a stable and nurturing home, lack of exposure to violence, full assessment for disabilities and adequate provision of appropriate education, therapies, and social services. Prevention of FASD and early identification and interventions for children with an FASD is essential and has become an important goal of the CDC and other organizations.

Fig. 146.5 Characteristic hand findings that can be seen in a child with an FASD: curved fifth finger (clinodactyly) and upper palmar crease that widens after the bend and ends between the second and third fingers ("hockey stick" crease). (*Courtesy Darryl Leja, NHGRI, National Institutes of Health.*)

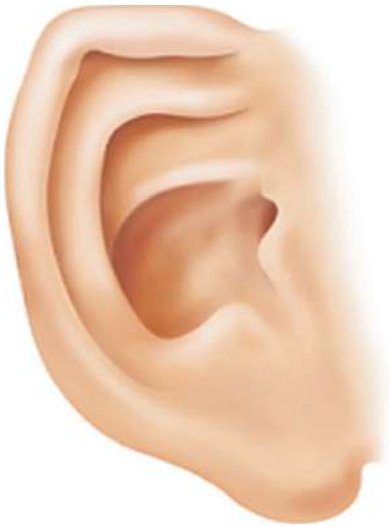

Fig. 146.6 Ear findings that can be seen in a child with an FASD: "railroad track" appearance of ear creases. (*Courtesy Darryl Leja, NHGRI, National Institutes of Health.*)

Table 146.1 Diagnostic Criteria for Fetal Alcohol Syndrome

ALL of the following, *with or without* documented prenatal alcohol exposure:

Facial features (Hoyme system requires two or more, 4-Digit Diagnostic Code requires all three):
- Palpebral fissures ≤10th percentile (Hoyme system) or ≤3rd percentile (4-Digit code)
- Thin upper lip (ranking of 4 or 5 on racially normed Lip-Philtrum Guide*)
- Smooth philtrum (ranking of 4 or 5 on racially normed Lip-Philtrum Guide*)

Prenatal and/or postnatal growth deficiency:
- Height and/or weight ≤10% for age and sex at any point of time (prenatal or postnatal)
- Adjust for gestational age if preterm. (4-Digit Diagnostic Code puts emphasis on short stature)

Deficient brain growth, abnormal brain formation or neurophysiology: one or more of following:
- Head circumference ≤10th % (Hoyme system) or ≤3rd percentile (4-Digit Diagnostic Code)
- Structural brain abnormalities
- Recurrent nonfebrile seizures with other causes excluded (Hoyme system)

Neurobehavioral impairment:
- For children <3 y/o: Developmental delay ≥1.5 SD below the mean
- For children 3 y/o or older (either of the following):
  - Cognitive impairment: Scores ≥1.5 SD below mean (Hoyme) or ≥2 SD below mean (4-Digit Diagnostic Code) either for global abilities or for at least one neurobehavioral domain (executive function, specific learning impairment, memory impairment, or visual-spatial impairment). The Hoyme system defines impairment domain as normal or abnormal. The 4-Digit Diagnostic Code has three domains defined: normal, moderate, severe.
  - Behavioral impairment without cognitive impairment: ≥1.5SD below mean in self-regulation (mood or behavioral regulation), attention deficit, or impulse control.

*The Hoyme system and the 4-Digit Diagnostic Code have different Lip-Philtrum Guides.
SD, Standard deviation.

INTERVENTIONS AND TREATMENTS

Given the heterogeneity of presenting problems associated with the FASDs, interventions need to be tailored to address each individual child's or adolescent's profile of strengths and difficulties. Studies support that the most successful interventions begin early and continue across the life span, include a preventive focus, are intensive and individualized, address multiple domains of functioning, include parent education and training, and are coordinated across systems of care.

Behavioral issues seen in children with FASD can be difficult for parents to manage and can cause significant stress within the home. These children often have impaired cause-and-effect understanding and therefore may not respond to traditional behavior modification strategies. Pediatricians can help support families by providing parenting tips suggested by the CDC, such as providing a structured environment and stable routines, using simple concrete language and lots of repetition, viewing the difficult behaviors as brain based rather than willful misbehavior, focusing on strengths, and providing an abundance of positive reinforcement. Specific programs include *Families Moving Forward* and *Parents and Children Together* teaching parents strategies designed to improve self-regulation and executive function, and decreasing child behavior problems. Children with FASD often have significant difficulties with social functioning, such as interpreting social cues and communicating in social settings. Programs such as *Children's Friendship Training* provides group-based, parent-assisted intervention that teaches social skills, which have been shown to improve standardized rating of social skills. Programs such as *Good Buddies* provide classes that address issues related to impaired social skills. Children with FASD may have decreased safety awareness, poor judgement, and impulsivity, which can place them at increased risk for unintentional injuries. A video-based intervention, *Fire and Street Safety,* was developed to address this. Children who participated showed significant improvement in safety-related knowledge and appropriate behavioral responses following the training and were also able to apply this training to real-world situations.

Young children with FASD are generally eligible for early intervention therapies (occupational therapy, physical therapy, speech therapy, and developmental instruction) and should be referred for these services as needed. Older children with an FASD often have difficulties with verbal and spatial learning, executive functioning, adaptive skills, social skills and peer relations, and mental health, which can interfere with academic performance. High rates of school failure and disruption are reported for this population. Difficulties with memory often require simplification of instructions, repetition, and patience. A home and school environment that is structured and predictable can also help to address this issue. To enhance generalizability of skills and to ensure they are encoded into memory, children with an FASD require consistent and predictable interventions, simplified directions, repeated instructions, and reduced distractions in the classroom. Classroom intervention programs such as *Cognitive Control Therapy* have been found to result in significant improvements in classroom behavior and academic achievement. Programs have also been developed that

Table 146.2 Diagnostic Criteria for Partial Fetal Alcohol Syndrome

- WITH documented prenatal alcohol exposure (requires A and B):
  - A. Facial features (at least two of three)
  - B. Neurobehavioral impairment (same as for FAS), i.e., leaves out brain abnormalities and growth deficiency
- WITHOUT documented prenatal alcohol exposure (requires A, B, and C):
  - A. Facial features (at least two of three)
  - B. Growth deficiency OR deficient brain growth/structural brain abnormalities/recurrent seizures (at least one of these)
  - C. Neurobehavioral impairment (same as for FAS), i.e., same as FAS except it is EITHER growth deficiency OR brain growth/structural brain abnormalities/recurrent seizures (does not require both)

Note that the diagnosis of FAS and pFAS are the only FASDs that can be diagnosed in the absence of a confirmed maternal history of PAE.

FAS, Fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome.

Table 146.3 Diagnostic Criteria for Alcohol-Related Neurodevelopmental Disorder

Requires A *and* B:

Note: *Cannot* be diagnosed definitively in children <3 yr old

A. Documented prenatal alcohol exposure

B. Neurobehavioral impairment:
- WITH cognitive impairment: Global delay OR deficit in at least TWO neurobehavioral domains (executive function, specific learning impairment, memory impairment, visual-spatial impairment)
- WITHOUT cognitive impairment: Behavioral deficit in at least TWO domains (behavioral regulation, attention, impulse control)

Table 146.4 Diagnostic Criteria for Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure

ND-PAE is a mental health disorder (rather than a medical disorder) included in the DSM-5 (2013) as a "new clarifying term" that encompasses the range of developmental disabilities associated with PAE that affect function and are not due to other conditions. This diagnosis requires:
- ≥1 deficit in neurocognition
- ≥2 deficits in adaptive functioning (at least one in communication or social communication and interaction)
- ≥1 deficit in self-regulation
- History of maternal consumption of more than 13 alcoholic drinks in any 30-day period of the pregnancy or more than 2 alcoholic drinks in one sitting
- Onset of the disorder in childhood
- The findings cause clinically significant distress or impairment in important areas of functioning and are not better explained by other causes (medication, medical conditions, genetic disorders, or environmental neglect)

Although the diagnosis of ND-PAE overlaps with ARND, ND-PAE aims to describe the *behavioral and mental health effects* on an individual with PAE. Unlike ARND, a diagnosis of ND-PAE can be given with or without the physical characteristics of FAS (ARND does not include physical characteristics) and the diagnosis of ND-PAE can be given in addition to FAS or pFAS.

ARND, Alcohol-related neurodevelopmental disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; FAS, fetal alcohol syndrome; ND-PAE, neurobehavioral disorder associated with prenatal alcohol exposure; pFAS, partial fetal alcohol syndrome.

address specific areas of learning, such as *Language and Literacy Training Math Interactive Learning Experience*. A cognitive-based intervention, the *Alert Program* has been adapted to address self-regulation and executive function difficulties in children with FAS or ARND living in foster care or adoptive homes. A video game, *GoFar*, was developed by to address issues of self-regulation. An intervention that uses rehearsal training interventions has been shown to result in improvement in working memory. Children with FASD have been found to show deficits in adaptive functioning more significant than expected based on their cognitive testing. Occupational therapy to address this issue can help to decrease the significant level of supervision and support required of parents and caregivers.

Table 146.5 Alcohol-Related Birth Defects

This diagnosis refers to a pattern of structural birth defects and other congenital abnormalities that can be characteristic of FASD.

Requires both A *and* B

A. Documented prenatal alcohol exposure

B. One or more specific major malformations found to be the result of prenatal alcohol exposure:
- Cardiac: ASD, VSD, aberrant great vessels, conotruncal heart defects
- Skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis
- Renal: kidney/ureteral malformations
- Eyes: strabismus, ptosis, retinal vascular abnormalities, optic nerve hypoplasia
- Ears: conductive or neurosensory hearing loss

ASD, Atrial septal defect; FASD, fetal alcohol spectrum disorder; VSD, ventricular septal defect.

There are no medications that are approved specifically for FASDs, but some medications may be used for symptom management. These can include stimulants (for hyperactivity, inattention, and poor impulse control), antidepressants, neuroleptics, and antianxiety drugs. Children with an FASD are often treated with a higher number of drugs and at higher doses, likely because of atypical or less favorable responses. Such atypical responses may require an adjustment in medication or discontinuation. Stimulant medication use in patients with FASD is controversial but is often considered, since there is a high prevalence of ADHD-like symptoms in this population. Stimulants can lead to some improvement in hyperactivity but may be less helpful for impulsivity and attention, and the rate of efficacy in general is not as high as in idiopathic ADHD. A diagnosis in the FASD spectrum should, in fact, be considered in a child with ADHD who has an atypical response to such medications. The efficacy of nonstimulant medications used for ADHD, such as alpha-2 agonists is being studied and may be shown to be helpful. Studies are also underway for use of choline supplementation and treatment with atomoxetine (a selective norepinephrine reuptake inhibitor). Data regarding the use of SSRI (selective serotonin reuptake inhibitors) medications, antipsychotics, and mood stabilizers are limited in terms of efficacy and safety.

THE PEDIATRICIAN/PRIMARY CARE PROVIDER'S ROLE

Pediatricians and other primary care providers need to document findings related to PAE and refer the child for a full evaluation. Indications for referral for further evaluation for FASD include confirmed history of significant PAE, concern raised by the caregiver about the possibility of FASD, all three facial features present, one or more facial features plus growth deficits, and one or more facial features along with one or more CNS abnormalities ± growth deficits. Evaluation for an FASD is best done by a multidisciplinary team that can provide a medical, genetic, and neuropsychologic assessment. This team might include a developmental behavioral pediatrician, psychologist/psychiatrist, geneticist, social worker, speech therapist, occupational therapist, physical therapist, and educational therapist/special education teacher. Evaluations by audiology and ophthalmology should be included if not already completed.

Once a diagnosis of an FASD is made, the pediatrician's/primary care providers role is important in establishing a medical home for the child that provides coordinated care between medical and mental health professionals, therapists, and educators who can help and support the child and family. The American Academy of Pediatrics (AAP) has developed an FASD toolkit (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/fetal-alcohol-spectrum-disorders-toolkit/Pages/default.aspx) that includes a "Flow Diagram for Medical Home Evaluation of Fetal Alcohol Spectrum Disorders" to assist primary care providers in identifying children with an FASD and managing their challenges in an effort to reduce the lifelong adverse consequences.

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Chapter 147

Infants of Diabetic Mothers

Kesi C. Yang

Diabetes (type 1, type 2, or gestational) in pregnancy increases the risk of complications and adverse outcomes in the mother and the baby. Complications related to diabetes are milder in gestational vs pregestational (preexisting type 1 or type 2) diabetes. Pregnancy outcomes are correlated with onset, duration, and severity of maternal hyperglycemia. Preconception planning and tight glycemic control (hemoglobin A_{1c} [HbA_{1c}] <6.5%) is crucial in pregestational diabetes to achieve the best outcomes for the mother and the baby. The risk of **diabetic embryopathy** (neural tube defects, cardiac defects, caudal regression syndrome) and spontaneous abortions is highest in those with pregestational diabetes who have poor control (HbA_{1c} >7%) in the first trimester. The risk of congenital malformations in **gestational diabetes** is only slightly increased compared to the general population, because the duration of diabetes is less and hyperglycemia occurs later in gestation (typically >25 weeks).

Mothers with pregestational and gestational diabetes have a high incidence of complications during the pregnancy. Polyhydramnios, preeclampsia, preterm labor (induced and spontaneous), and chronic hypertension occur more frequently in mothers with diabetes. Accelerated fetal growth is also common, and 36–45% of **infants of diabetic mothers (IDMs)** are born large for gestational age (LGA). Restricted fetal growth is seen in mothers with pregestational diabetes and vascular disease, but it is less common. Fetal mortality rate is greater in both pregestational and gestational diabetic mothers than in nondiabetic mothers, but the rates have dropped precipitously over the years. Fetal loss throughout pregnancy is associated with poorly controlled maternal diabetes, especially **diabetic ketoacidosis**. The neonatal mortality rate of IDMs is >5 times that of infants of nondiabetic mothers and is higher at all gestational ages and in every birthweight for gestational age category. The rate is higher in women with pregestational diabetes, smoking, obesity, hypertension, and poor prenatal care.

PATHOPHYSIOLOGY

The probable pathogenic sequence is that maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia, or hyperinsulinism. It is important to recognize that while maternal glucose crosses the placenta, maternal and exogenous insulin does not. Fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis (Fig. 147.1). Related pathologic findings are hypertrophy and hyperplasia of the pancreatic β cells, increased weight of the placenta and infant organs (except the brain), myocardial hypertrophy, increased amount of cytoplasm in liver cells, and extramedullary hematopoiesis. Hyperinsulinism and hyperglycemia produce fetal acidosis, which may result in an increased rate of stillbirth. Separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on hyperinsulinism, leading to hypoglycemia during the first few hours after birth. The risk of rebound hypoglycemia can be diminished by tight blood glucose control during labor and delivery.

Hyperinsulinemia has been documented in infants of mothers with pregestational and gestational diabetes. The infants of mothers with *pregestational* diabetes have significantly higher fasting plasma insulin levels than normal newborns, despite similar glucose levels, and respond to glucose with an abnormally prompt elevation in plasma insulin. After arginine administration, they also have an enhanced insulin response and increased disappearance rates of glucose compared with normal infants. In contrast, fasting glucose production and utilization rates are diminished in infants of mothers with *gestational* diabetes. Although hyperinsulinism is probably the main cause of hypoglycemia, the diminished epinephrine and glucagon responses that occur may be contributing factors. Infants of mothers with pregestational and gestational diabetes are at risk for neonatal hypoglycemia in the first hours of life, with an increased risk in both large- and small-for-gestational-age infants. Aggressive screening and treatment is recommended as outlined later.

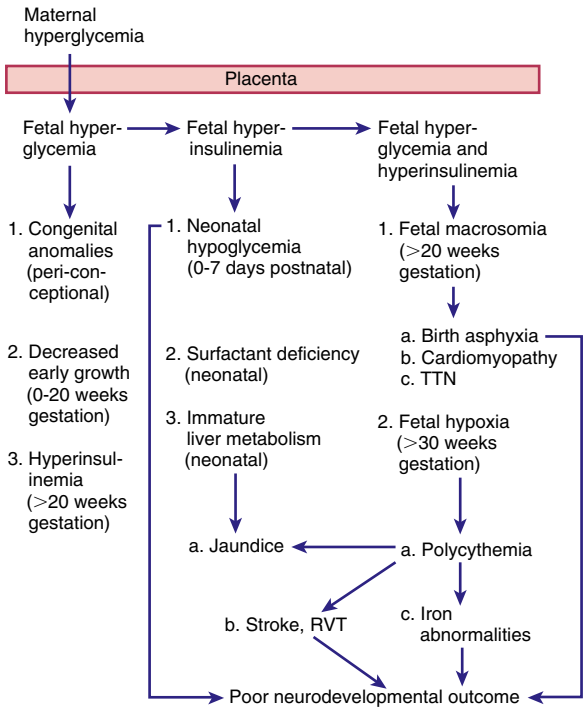

Fig. 147.1 The fetal and neonatal events attributable to fetal hyperglycemia *(column 1)*, fetal hyperinsulinemia *(column 2)*, or both in synergy *(column 3)*. Time of risk is denoted in parentheses. RVT, Renal vein thrombosis; TTN, transient tachypnea of the newborn. (*From Nold JL, Georgieff MK. Infants of diabetic mothers. Pediatr Clin North Am. 2004;51:619–637.*)

CLINICAL MANIFESTATIONS

Infants of mothers with pregestational diabetes and those of mothers with gestational diabetes often bear a surprising resemblance to each other (Fig. 147.2). They tend to be macrosomic as a result of increased body fat and enlarged viscera, with puffy, plethoric facies resembling those of patients who have been receiving corticosteroids. These infants may also be of normal birthweight if diabetes is well controlled or low birthweight if they are delivered before term or if their mothers have associated diabetic vascular disease. Infants that are macrosomic or LGA are at high risk of birth trauma (brachial plexus injury) and birth asphyxia because of not only their large size but also their decreased ability to tolerate stress, especially if they have cardiomyopathy and other effects of fetal hyperinsulinemia (Table 147.1).

Hypoglycemia develops in approximately 25–50% of infants of mothers with pregestational diabetes and 15–25% of infants of mothers with gestational diabetes, but only a small percentage of these infants become symptomatic. The probability that hypoglycemia will develop in such infants increases with higher cord or maternal fasting blood glucose levels. The nadir in an infant's blood glucose concentration is usually reached between 1 and 3 hours of age. Hypoglycemia can persist for 72 hours and in rare cases last up to 7 days. Frequent feedings can be used to treat the hypoglycemia, but some infants require intravenous (IV) dextrose.

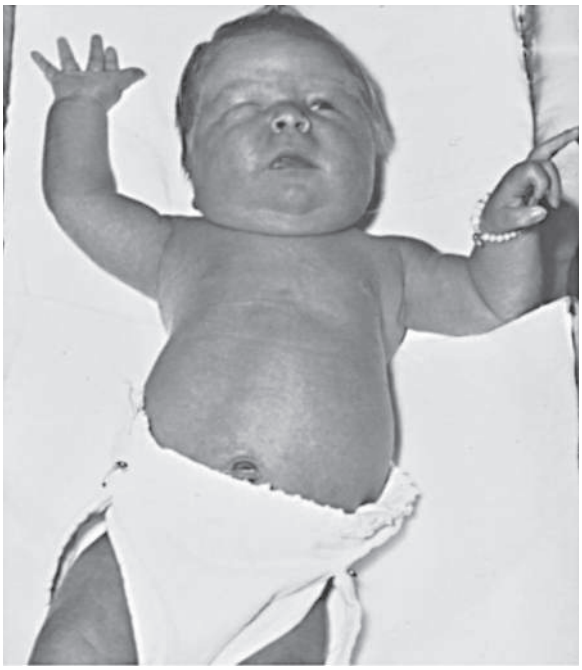

Fig. 147.2 Macrosomic, plethoric infant of a mother with gestational diabetes. The baby was born at 38 weeks of gestation but weighed 9 lb, 11 oz (4,408 g). Mild respiratory distress was the only symptom other than appearance.

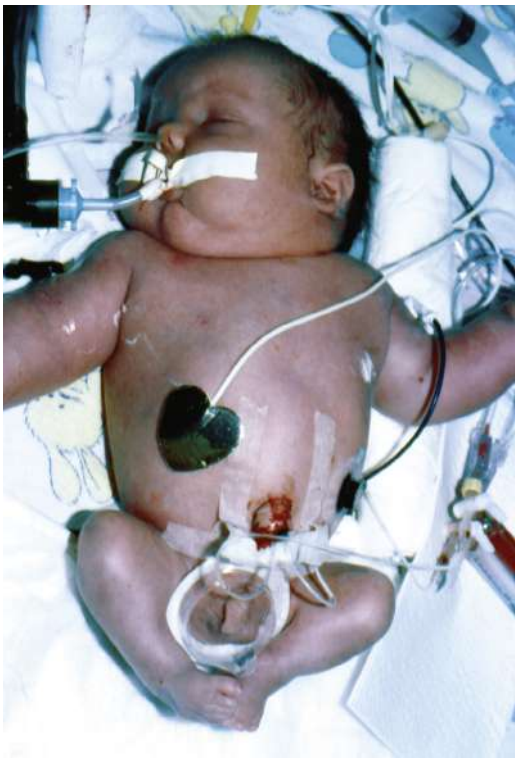

Fig. 147.3 Caudal dysplasia sequence. Newborn male infant with a normal upper body and a short lower segment. (*Modified from Jones KL, Jones MC, Del Campo M, eds. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022: Fig. 1, p. 897.*)

Table 147.1 Morbidity in Infants of Diabetic Mothers

Congenital anomalies
Heart failure and septal hypertrophy of heart
Surfactant deficiency, respiratory distress syndrome, transient tachypnea of the newborn, persistent pulmonary hypertension
Hyperbilirubinemia
Hypoglycemia, hypocalcemia, hypomagnesemia
Macrosomia, nerve injury related to birth trauma
Renal vein thrombosis
Small left colon
Unexplained intrauterine demise
Polycythemia
Visceromegaly
Predisposition to later-life obesity, insulin resistance, and diabetes

From Devaskar SU, Garg M. Disorders of carbohydrate metabolism in the neonate. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine*, 10th ed. Philadelphia: Elsevier; 2015: Box 95-3.

The infants tend to be jittery, tremulous, and hyperexcitable during the first 3 days after birth, although hypotonia, lethargy, and poor feeding may also occur. Early appearance of these signs is more likely to be related to hypoglycemia but can also be caused by hypocalcemia and hypomagnesemia, which also occur in the first 24-72 hours of life due to delayed response of the parathormone system. Perinatal asphyxia is associated with increased irritability and also increases the risk of hypoglycemia, hypomagnesemia, and hypocalcemia.

Tachypnea develops in many IDMs during the first 2 days after birth and may be a manifestation of hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia. IDMs have a higher incidence of **respiratory distress syndrome** (RDS) than do infants of nondiabetic mothers born at comparable gestational age. The greater incidence is likely related to an inhibitory effect of insulin on surfactant protein expression. **Polycythemia** often occurs with RDS as they are both a result of fetal hyperinsulinism.

Cardiomegaly is common, and heart failure occurs in 5–10% of IDMs. Interventricular septal hypertrophy may occur and may manifest as **transient idiopathic hypertrophic subaortic stenosis**. This is thought to result from chronic hyperglycemia and chronic hyperinsulinism leading to glycogen loading in the heart. Inotropic agents worsen the obstruction and are contraindicated. β-Adrenergic blockers have been shown to relieve the obstruction, but ultimately the condition resolves spontaneously over time.

Acute neurologic abnormalities (lethargy, irritability, poor feeding) can be seen immediately after birth. The symptoms will resolve with treatment of the underlying cause but may persist for weeks if caused by birth asphyxia. Neurologic development and ossification centers tend to be immature and to correlate with brain size (which is not increased) and gestational age rather than total body weight in infants of mothers with gestational and pregestational diabetes. In addition, IDMs have an increased incidence of hyperbilirubinemia, polycythemia, iron deficiency, and renal vein thrombosis. Renal vein thrombosis should be suspected in the infant with a flank mass, hematuria, and thrombocytopenia.

There is a fourfold increase in **congenital anomalies** in infants of mothers with pregestational diabetes, and the risk varies with HbA_{1c} during the first trimester when organogenesis occurs. The recommended goal for periconceptual HbA_{1c} is <6.5%. Although the risk of congenital malformations increases with increasing HbA_{1c} levels, there may still be an increased risk in the therapeutic goal range. Congenital anomalies of the central nervous system and cardiovascular system are most common, including failure of neural tube closure (encephalocele, meningomyelocele, and anencephaly), transposition of great vessels, ventricular septal defect (VSD), atrial septal defect (ASD), hypoplastic left heart, aortic stenosis, and coarctation of the aorta. Other less common anomalies include caudal regression syndrome (Fig. 147.3), intestinal atresia, renal agenesis, hydronephrosis, and cystic kidneys. **Small left colon syndrome** is a rare anomaly that develops in the second and third trimester because of rapid fluctuations in maternal and therefore fetal glucose, leading to impaired intestinal motility and subsequent intestinal growth. Prenatal ultrasound and a thorough newborn physical examination will identify most of these anomalies. High clinical

suspicion and a good prenatal history will help identify needed screening for subtle anomalies.

TREATMENT

Preventive treatment of IDMs should be initiated before birth by means of preconception and frequent prenatal evaluations of all women with preexisting diabetes and pregnant women with gestational diabetes. This involves evaluation of fetal maturity, biophysical profile with nonstress testing (NST), Doppler velocimetry, and planning of the delivery of IDMs in hospitals where expert obstetric and pediatric care is continuously available. Preconception glucose control reduces the risk of anomalies and other adverse outcomes in women with pregestational diabetes, and glucose control during labor reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy (average daily glucose levels <95 mg/dL and $HgbA_{1c}$ <6.5%, if safely achievable without hypoglycemia) deliver infants with birthweight and anthropomorphic features similar to those of infants of nondiabetic mothers. Treatment of gestational diabetes (diet, glucose monitoring, insulin, and oral antihyperglycemic treatment with metformin or glyburide as needed) decreases the rate of serious perinatal outcomes (death, shoulder dystocia, bone fracture, or nerve palsy). Continuous glucose monitoring has been increasingly used in pregnancy to achieve these purposes. In these mothers, the incidence of macrosomia and neonatal hypoglycemia is similar to that in mothers with insulin-treated gestational diabetes.

Regardless of size, IDMs should initially receive close observation and care. All infants should initiate feedings within 1 hour after birth. A screening glucose test should be performed no sooner than 30 minutes of life but no later than 2 hours and should be performed immediately in symptomatic infants. Defining precise glucose thresholds in neonates remains a challenge. The American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES) have both published guidelines based on observational data and expert opinion. These guidelines are adapted within individual institutions, with one example included in Figure 147.4. The AAP recommends maintaining a blood glucose level greater than 40 mg/dL (2.2 mmol/L) in the first 4 hours of life and greater than 45 mg/dL in the first 4 to 24 of life (2.5 mmol/L). In comparison, the PES recommends maintain a threshold of greater than 50 mg/dL (2.8 mmol/L) in the first 48 hours.

Feeding is the initial treatment for *asymptomatic* hypoglycemia. Oral or gavage feeding with breast milk or formula per maternal preference can be given. **Dextrose gel** has been shown to be a safe and

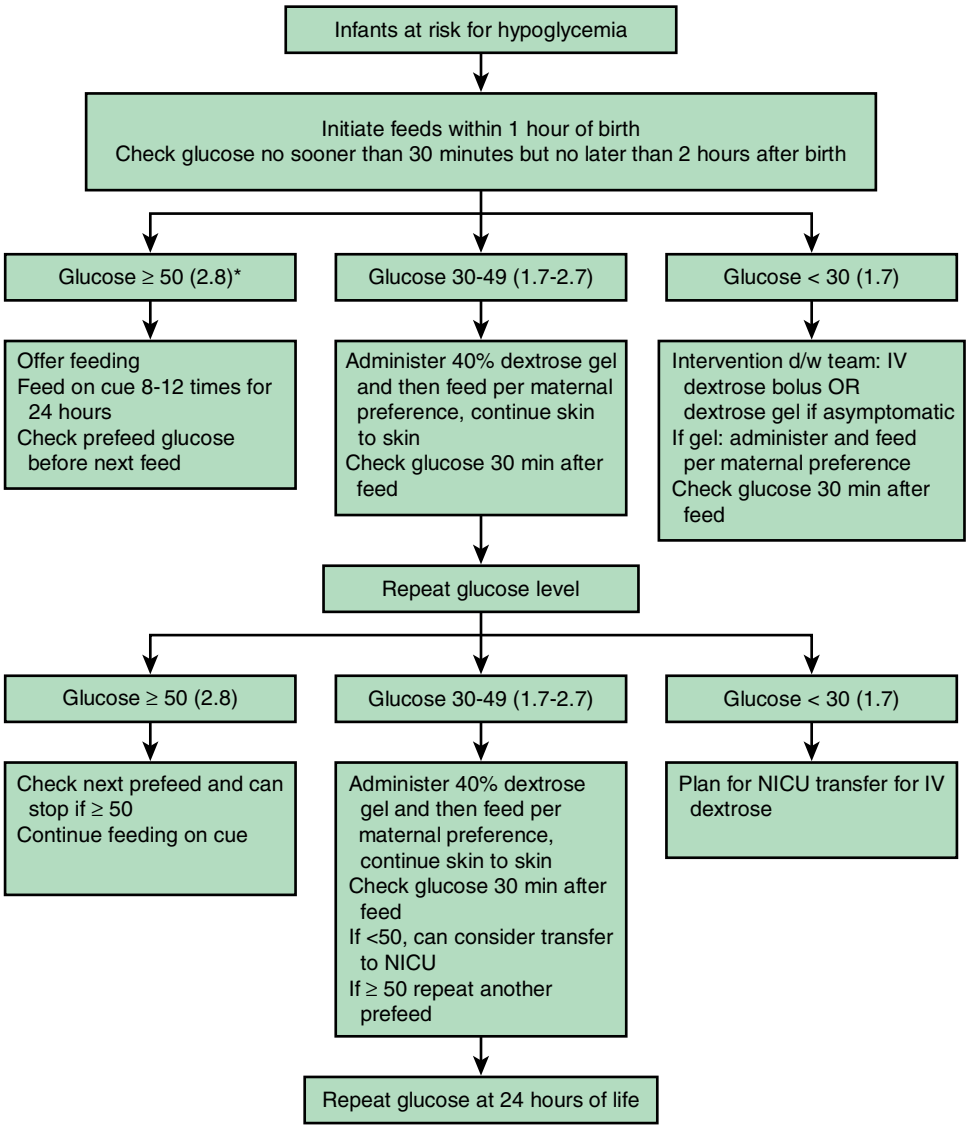

Fig. 147.4 Neonatal hypoglycemia algorithm at the Hospital of the University of Pennsylvania. This was derived from institutional consensus and meant to serve as a sample management protocol as there is no defined threshold for neonatal hypoglycemia in the first day of life. IV, Intravenous; NICU, neonatal intensive care unit. *Units are mg/dL (mmol/L).

effective adjunct to feeding and should be administered if available. Infants with *persistent* (and unresponsive to oral therapy) hypoglycemia should be treated with IV glucose (bolus followed by continuous infusion), especially if symptomatic. If question arises about an infant's ability to tolerate oral feeding, a continuous peripheral IV infusion at a rate of 4-8 mg/kg/min should be given. Neurologic symptoms of hypoglycemia *must* be treated with IV glucose. Bolus injections of hypertonic (25%) glucose should be avoided because they may cause further hyperinsulinemia and potentially produce rebound hypoglycemia (see Chapter 113). For treatment of hypocalcemia and hypermagnesemia, see Chapters 121.4 and 121.5; for RDS treatment, see Chapter 126; and for treatment of polycythemia, see Chapter 141.

PROGNOSIS

The subsequent incidence of diabetes mellitus in IDMs is higher than that in the general population because of genetic susceptibility in all types of diabetes. Infants of mothers with either pregestational diabetes or gestational diabetes are at risk for obesity and impaired glucose metabolism in later life as a result of intrauterine exposure to hyperglycemia. Disagreement persists about whether IDMs have a slightly increased risk of impaired intellectual development because of the many confounding factors (e.g., parental education, maternal age, neonatal complications). In general, the outcomes have improved over the last several decades due to increased awareness, screening, and improved prenatal care for pregnant women with diabetes.

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Chapter 148

Epidemiology of Infections

Dustin D. Flannery

Neonatal infections are often classified by their timing relative to birth and include congenital, perinatal, early-onset, and late-onset disease. This categorization is clinically useful because infectious mechanisms, etiologies, and outcomes are fairly distinct for each, although there is some overlap between the different types. **Congenital infection** denotes infection acquired in utero. Such infections are often associated with injury to developing organs, depending on the timing of infection during gestation (see Chapter 149). **Perinatal infection** indicates acquisition around the time of delivery. Perinatally acquired organisms include both bacteria and viruses, some of which are the same as those causing congenital infection, but often manifest with different features. **Early-onset infection** occurs in the first 3 days after birth and is generally the consequence of infection caused by organisms acquired during the perinatal period. **Late-onset infection** occurs after 3 days and is caused by organisms that are typically acquired in the postnatal period. Notably, some studies categorize early-onset and late-onset infections as within the first 7 days of age and after 7 days, respectively, particularly for infants not continuously admitted to the hospital from birth, who are exposed to pathogens in the community.

Neonates are prone to infection for multiple reasons, namely because of their lack of fully responsive innate immunity (Fig. 148.1). Attenuated immune responses often result in minimal or nonspecific clinical manifestations, and effective treatment requires attention to subtle signs of infection and known risk factors. Compared with older infants, neonates are often treated empirically with systemic antimicrobials while awaiting results of laboratory investigations. Preterm infants are particularly susceptible to infection because of their decreased innate immune and barrier defenses, need for invasive medical devices such as central venous catheters, and prolonged hospitalizations. The term "neonatal sepsis" typically refers to culture-confirmed infection of the blood, cerebrospinal fluid, and/or urine, though definitions vary across studies.

INCIDENCE

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. Neonatal infections are more common in areas with limited access to healthcare than in areas with a well-established healthcare infrastructure. Estimated incidence rates vary based on the case definition, geographical region, and the population studied. The overall global incidence of neonatal sepsis and other severe infections remains unknown given the lack of data from many countries, though the disease is common and often fatal. The global incidence is estimated at 2,824 cases per 100,000 live births; ~18% are fatal. For congenital infections, the incidence varies greatly depending on the specific infectious etiology and geographic region, though low- and middle-income countries have the greatest burden of disease.

The overall incidence of early-onset infection in the United States is approximately 1 per 1,000 live births and is dramatically higher among infants born preterm. The incidence varies significantly by gestational age (GA) and is highest among infants with a GA of 22 to 28 weeks (18.5 cases per 1,000 births). A 2021 report of over 84,000 very preterm infants at centers in the United States estimated the incidence of early-onset infection at 13.5 per 1,000 births; the incidence again varied substantially by GA (Table 148.1) and was highest for infants born <24 weeks (45.4 per 1,000 births). Similar to early-onset infection, late-onset infection incidence is inversely related to the degree of prematurity with significant variation across centers and geography. Among hospitalized newborns, 0.6–14% develop late-onset infection, with up to 40% of very preterm infants suffering from at least one episode.

MICROBIOLOGY

Infection microbiology is critically important to inform preventative strategies, as well as empiric and targeted antimicrobial therapies. A number of bacterial and nonbacterial pathogens can infect fetuses and newborns. Although there is overlap, pathogen types may be distinguished by timing of infection (Table 148.2).

The TORCH pneumonic, although not all-encompassing, is used to describe common causes of most often congenital or perinatal but also postnatal infection (see Table 148.2): toxoplasmosis, *Treponema pallidum* (syphilis), rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, and other pathogens including parvovirus B19, varicella, and tuberculosis (TB). For pathogens causing congenital (prenatal), perinatal, and postnatal infection, modes of transfer include transplacental infection, exposure during labor and delivery through an infected or colonized birth canal, or from contact with an infected caretaker and/or infected breast milk (see Chapter 149). Some viral infections (e.g., CMV) can be substantial causes of disease whether acquired during gestation or acquired postpartum, whereas others (e.g., respiratory syncytial virus) are typically acquired only in the postnatal period (Fig. 148.2).

The two most common bacterial causes of **early-onset infection** are group B *Streptococcus* (GBS) and *Escherichia coli*; GBS is most common among term infants, whereas *E. coli* is the predominant pathogen among preterm infants. Approximately 30% of early-onset infections are caused by organisms other than GBS or *E. coli* (see Table 148.2). Coagulase-negative staphylococci (CONS) are the predominant cause of **late-onset infection** in hospitalized neonates, often accounting for 50–80%. Other common causes (see Table 148.2) include *Staphylococcus aureus*, gram-negative bacilli (*E. coli, Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp.), and fungi (*Candida* spp.). In Asia and Africa additional pathogens cause early-onset sepsis (*Acinetobacter* spp., *Klebsiella pneumoniae*); these pathogens are often resistant to first-line antibiotics.

Microorganisms causing pneumonia acquired during labor and delivery include GBS, gram-negative enteric aerobes, *Listeria monocytogenes,*

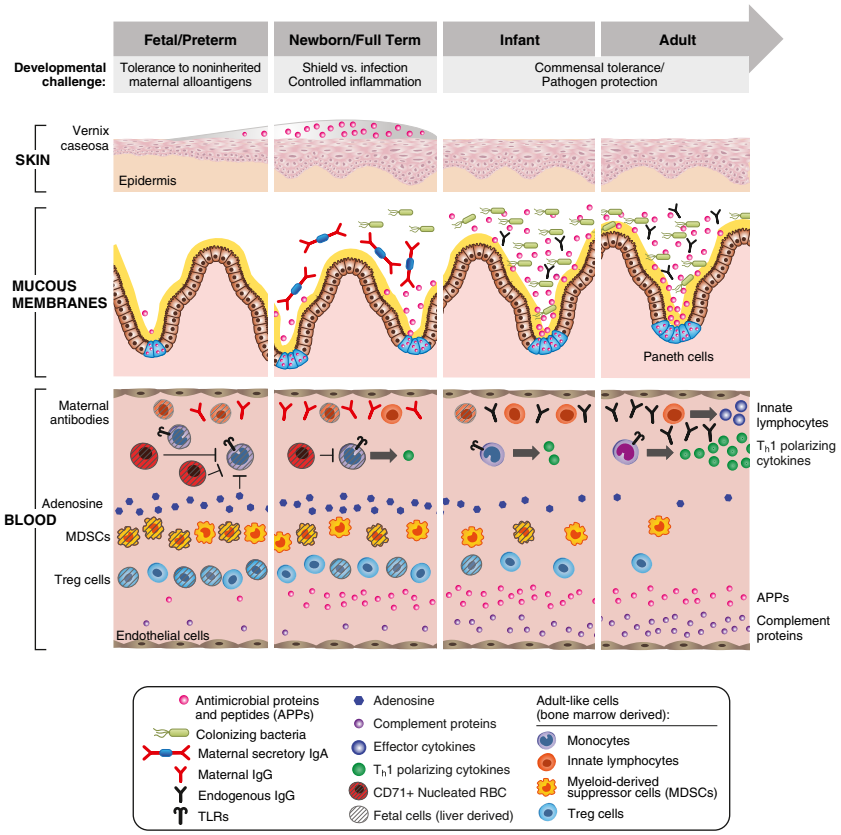

Fig. 148.1 Ontogeny of skin, soluble, and cellular innate defense systems. Host-protective barrier functions include physical, chemical, and functional components of the skin and mucous membrane epithelia of the fetus, neonate (birth to 28 days of age), and infant (1 month to 1 year of age). Skin: while physical and chemical barriers are impaired in early in life, especially in the preterm newborn, the vernix caseosa and skin epithelia of full-term newborns robustly express antimicrobial proteins and peptides (APPs). Mucous membranes: in parallel with and induced by an increasingly complex microbiota, the newborn intestinal mucosal epithelium rapidly changes structurally, with an increase in the population of crypts and crypt-based Paneth cells, as well as functionally with increasing APP expression. Blood: the composition of neonatal blood is distinct, with relatively low concentrations of complement components and APPs and high concentrations of the immunosuppressive purine metabolite adenosine. Plasma also contains maternal antibodies that are transferred beginning midgestation and supplemented by postnatal factors derived from breast milk. Innate immunity is detectable from the end of the first month of gestation, with changes driven largely by the increasing exposure to environmental microbes. Neonatal antigen-presenting cells such as blood monocytes express pattern recognition receptors (e.g., toll-like receptors [TLRs]) with distinct functional responses, including limited Th1-polarizing cytokine production, to most stimuli. Adaptive immunity develops from 4 weeks of gestation onward, with changes driven by an evolving chimerism reflecting fetal (liver-derived, *shaded cells*) regulatory T (Treg)-cell–rich lymphocytes, and more adultlike (bone marrow derived, *unshaded cells*) lymphocytes with distinct, epigenetically encoded functional programs. Ig, Immunoglobulin; RBC, red blood cell. *(Modified from Kollmann TR, Kampmann B, Mazmanian SK, et al. Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny. Immunity. 2007;46:350–363.)*

Table 148.1 Incidence of Early-Onset Infection Among Very Preterm Infants

CATEGORY	INCIDENCE RATE PER 1,000 BIRTHS (99% CI)
Overall	13.5 (12.5-14.6)
Gestational age, completed weeks	
≤23	45.4 (38.3-53.7)
24-25	26.0 (22.6-29.9)
26-27	15.5 (13.2-18.2)
28-29	10.1 (8.5-11.9)

Adapted from Flannery DD, Edwards EM, Puopolo KM, et al. Early-onset sepsis among very preterm infants. *Pediatrics.* 2021;148(4):e2021052456.

Mycoplasma, Chlamydia trachomatis, CMV, HSV, and *Candida* spp. (Table 148.3). The most common bacterial causes of neonatal meningitis are GBS, *E. coli, L. monocytogenes, Streptococcus pneumoniae,* other streptococci, *Haemophilus influenzae,* both coagulase-positive and coagulase-negative staphylococci, and other gram-negative bacilli. *Treponema pallidum* and TB infection involving the central nervous system (CNS) may also result in meningitis.

PATHOGENESIS

Early-Onset Infections

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extrauterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or

Table 148.2 Most Common Pathogens Causing Neonatal Infections, Grouped by Timing of Infection

CONGENITAL/PERINATAL
- Toxoplasmosis
- *Treponema pallidum* (syphilis)
- Rubella
- Cytomegalovirus
- Herpes simplex virus
- Hepatitis B and C
- Human immunodeficiency virus
- Varicella
- Parvovirus B19
- Tuberculosis
- Zika virus

EARLY-ONSET
- Group B *Streptococcus*
- *Escherichia coli*
- *Haemophilus* species
- *Staphylococcus aureus*
- *Klebsiella* species
- *Enterococcus* species
- Herpes simplex virus
- *Streptococcus anginosus*
- *Listeria monocytogenes*
- *Enterobacter* species
- *Citrobacter* species
- *Streptococcus pneumoniae*
- *Morganella morganii*
- *Pseudomonas* species
- *Serratia* species
- *Bacteroides* species

LATE-ONSET
- Coagulase-negative staphylococci
- *Staphylococcus aureus*
- *Escherichia coli*
- *Candida* species
- *Enterococcus* species
- *Group B Streptococcus*
- *Klebsiella* species
- *Enterobacter* species
- *Pseudomonas* species
- Respiratory syncytial virus
- Herpes simplex virus
- Enteroviruses
- *Listeria monocytogenes*

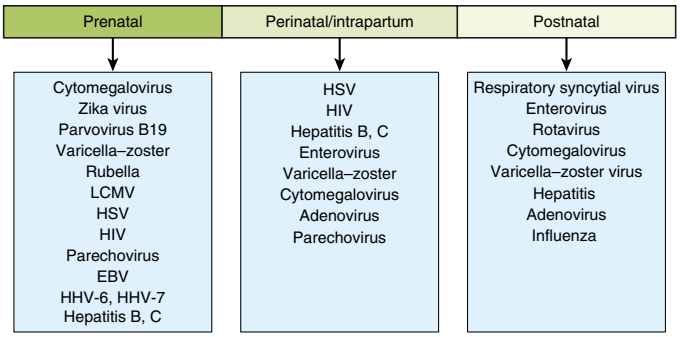

Fig. 148.2 Relative importance of neonatal viral infections related to the timing of acquisition of infection. Viruses are listed in declining order of importance relative to prenatal, perinatal (intrapartum), and postnatal timing of typical infection. Some neonatal virus infections (e.g., cytomegalovirus) can be substantial causes of disease whether acquired during gestation or acquired postpartum, whereas others (e.g., respiratory syncytial virus) are typically acquired in the postnatal period. EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus. *(From Schleiss MR, Marsh KJ. Viral infections of the fetus and newborn. In: Gleason CA, Juul SE, eds. Avery's Diseases of the Newborn. 10th ed. Philadelphia: Elsevier; 2018: Fig. 37.1.)*

colonization of the neonate at birth. Vertical transmission of agents that infect the amniotic fluid and vaginal canal, and contamination from the gastrointestinal tract, may occur in utero or, more often, during labor and delivery (Fig. 148.3).

Chorioamnionitis results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term *chorioamnionitis* refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis (uterine tenderness, foul-smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, diagnosed only by amniotic fluid analysis or pathologic examination of the placenta. The rate of histologic chorioamnionitis is inversely related to GA at birth (Fig. 148.4) and directly related to duration of membrane

Table 148.3 Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

TRANSPLACENTAL
Cytomegalovirus (CMV)
Herpes simplex virus (HSV)
Mycobacterium tuberculosis
Rubella virus
Treponema pallidum
Varicella-zoster virus (VZV)
Listeria monocytogenes

PERINATAL
Anaerobic bacteria
Chlamydia
CMV
Enteric bacteria
Group B *Streptococci*
Haemophilus influenzae
HSV
Listeria monocytogenes
Mycoplasma

POSTNATAL
Adenovirus
Candida spp.*
Coagulase-negative staphylococci
CMV
Enteric bacteria*
Enteroviruses
Influenza viruses A, B
Parainfluenza
*Pseudomonas**
Respiratory syncytial virus (RSV)
Staphylococcus aureus
Mycobacterium tuberculosis
Legionella

*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

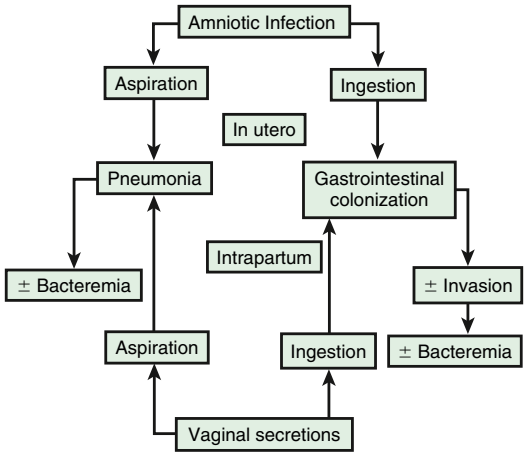

Fig. 148.3 Pathways of ascending or intrapartum infection.

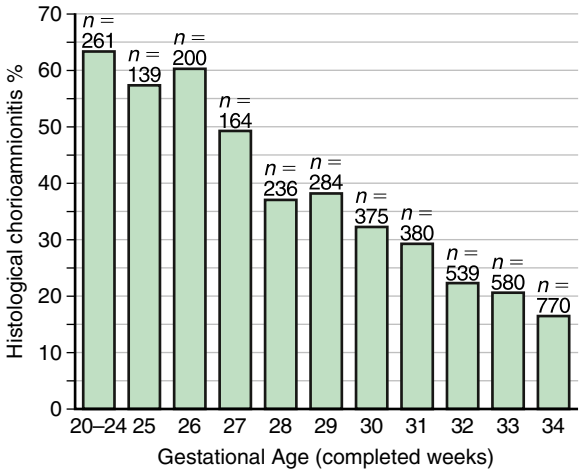

Fig. 148.4 Histologic chorioamnionitis in liveborn preterm babies by gestational age (n = 3,928 babies). *(From Lahra MM, Jeffery HE. A fetal response to chorioamnionitis is associated with early survival after preterm birth. Am J Obstet Gynecol. 2004;190:147–151.)*

rupture. Chorioamnionitis increases the risk of neonatal sepsis; however, most infants exposed to chorioamnionitis do not develop sepsis.

Chorioamnionitis was thought to result from infection of the amniotic fluid but is now better defined by the term *intrauterine inflammation* or *infection* at birth *(Triple I)*. This is defined by fetal tachycardia, maternal leukocytosis (>15,000 cells in the absence of corticosteroids), purulent fluid from the cervical os, biochemical or microbiologic amniotic fluid changes consistent with infection, and fever (≥39.0°C) (see Chapter 149.2).

Bacterial colonization does not always result in fetal or neonatal disease. Factors influencing which colonized infant will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies (Fig. 148.5). Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (apnea, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

Late-Onset Infections

After birth, neonates are exposed to infectious agents in the hospital or in the community (including family and caretakers). Postnatal infections may be transmitted by direct contact with hospital personnel, the mother, or other caretakers; from breast milk (e.g., HIV, CMV); or from inanimate sources such as contaminated equipment or surfaces. The most common source of postnatal infections in hospitalized newborns is *hand contamination* of healthcare personnel, underscoring the importance of hand hygiene. Contaminated milk, especially powdered formula *(Cronobacter sakazakii, Salmonella)*, equipment, other objects, or the environment are rare sources of neonatal infections but should be suspected during outbreaks of single organism disease.

Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or penetrating wounds from fetal scalp sampling or internal fetal electrocardiographic monitors. Cerebral abscess formation, ventriculitis, septic infarcts, hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children. Metabolic factors, including hypoxia, acidosis, hypothermia, and inherited metabolic disorders (e.g., galactosemia), are likely to contribute to risk for and severity of neonatal infection.

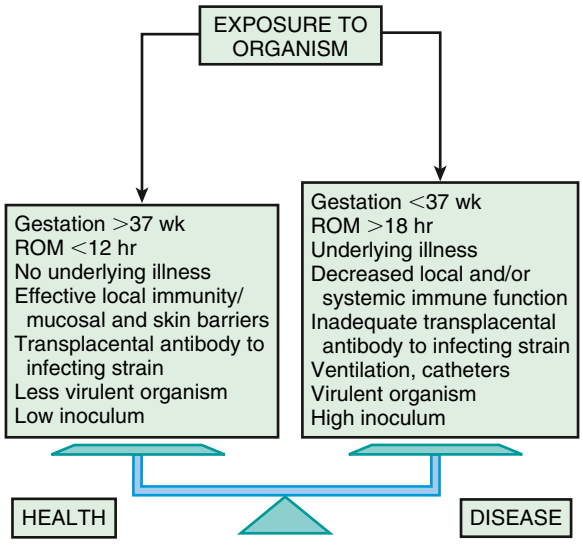

Fig. 148.5 Factors influencing the balance between health and disease in neonates exposed to a potential pathogen. ROM, Rupture of membranes. *(Adapted from Baker CJ. Group B streptococcal infections. Clin Perinatol 1997;24:59–70.)*

Infection in Premature Infants

The most important neonatal factors predisposing to infection are prematurity and low birthweight. Premature infants have a 3- to 10-fold higher incidence of infection than full-term normal birthweight infants. Possible explanations include the following: (1) maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn; (2) the frequency of intraamniotic infection is inversely related to GA (see Figs. 148.1 and 148.5); (3) premature infants have documented immune dysfunction; and (4) premature infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, putting them at continued risk for hospital-acquired infections.

CLINICAL MANIFESTATIONS

The maternal history and circumstances of delivery provide important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis). Signs and symptoms in the neonate are often subtle and nonspecific. Temperature instability, tachypnea, lethargy, apnea, and poor feeding are common initial signs and should raise suspicion for systemic or focal infection (Table 148.4).

Bacterial Sepsis

Neonates with bacterial sepsis may have either nonspecific manifestations or focal signs of infection (see Table 148.4), including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. Table 148.5 lists World Health Organization *international criteria* for sepsis. The initial manifestation may involve only limited symptomatology and only one system, such as apnea alone or tachypnea with retractions, or tachycardia, or the infant may present with an acute catastrophic manifestation

Table 148.4 Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL	**CARDIOVASCULAR**
Fever, temperature instability	Pallor; mottling; cold, clammy skin
Hypothermia	Tachycardia
"Not doing well"	Hypotension
Poor feeding	Bradycardia
Edema	
GASTROINTESTINAL	**CENTRAL NERVOUS**
Abdominal distention	Irritability, lethargy
Vomiting	Tremors, seizures
Diarrhea	Hyporeflexia, hypotonia
Hepatomegaly	Abnormal Moro reflex
	Irregular respirations
RESPIRATORY	Full fontanel
Apnea, dyspnea	High-pitched cry
Tachypnea, retractions	
Flaring, grunting	**HEMATOLOGIC**
Cyanosis	Jaundice
	Splenomegaly
RENAL SYSTEM	Pallor
Oliguria	Petechiae, purpura
	Bleeding

Table 148.5 Clinical Criteria for the Diagnosis of Sepsis in the International Setting: IMCI and WHO Criteria for Severe Infections in Children

- *Neurologic:* Convulsions, drowsy or unconscious, decreased activity, bulging fontanel
- *Respiratory*: Respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
- *Cardiac*: Poor perfusion, rapid and weak pulse
- *Gastrointestinal*: Jaundice, poor feeding, abdominal distention
- *Dermatologic*: Skin pustules, periumbilical erythema or purulence
- *Musculoskeletal*: Edema or erythema overlying bones or joints
- Other: Temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

IMCI, Integrated Management of Childhood Illness; WHO, World Health Organization. Adapted from WHO. *Pocket Book Of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses.* 2nd ed. Geneva: WHO. 2013. p 45–69. http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/.

with multiorgan dysfunction and shock. Infants should be reevaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).

A variety of noninfectious conditions can occur together with neonatal infection or can make the diagnosis of infection more difficult. Respiratory distress syndrome (RDS) secondary to surfactant deficiency can mimic and/or coexist with bacterial pneumonia in premature infants. Because bacterial sepsis can be rapidly progressive, the physician must be alert to the signs and symptoms of possible infection and must initiate diagnostic evaluation and empirical therapy in a timely manner for infants at risk. The differential diagnosis of many of the signs and symptoms that suggest infection is extensive; noninfectious disorders must also be considered (Table 148.6).

Systemic Inflammatory Response Syndrome

The clinical manifestations of infection depend on the virulence of the infecting organism and the body's inflammatory response. The term *systemic inflammatory response syndrome* (SIRS) is most frequently used to describe this unique process of infection and the subsequent systemic response (see Chapter 85). In addition to infection, SIRS may result from trauma, hemorrhagic shock, other causes of ischemia and inflammation, necrotizing enterocolitis, and pancreatitis.

Patients with SIRS have a spectrum of clinical symptoms that represent progressive stages of the pathologic process. In adults, SIRS is defined by the presence of two or more of the following: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea, and (4) abnormal white blood cell (WBC) count or an increase in immature forms. In neonates and pediatric patients, SIRS manifests as temperature instability, respiratory dysfunction (altered gas exchange, hypoxemia, acute RDS), cardiac dysfunction (tachycardia, delayed capillary refill, hypotension), and perfusion abnormalities (oliguria, metabolic acidosis) (Table 148.7). Increased vascular permeability results in capillary leak into peripheral tissues and the lungs, with resultant peripheral and pulmonary edema. DIC results in the more severely affected cases. The cascade of escalating tissue injury may lead to multisystem organ failure and death.

There are neonates who appear to have sepsis or SIRS but no bacterial or viral pathogen has been recovered. Culture negative sepsis may be due to a hard-to-culture bacteria (anaerobes) or virus, as well as noninfectious inflammatory conditions. In addition, an undetected localized source with transient bacteremia (osteomyelitis), prior antibiotic treatment, and poor culture technique (too small blood sample for culture may miss bacteremia) may be responsible.

Table 148.6 Serious Systemic Illness in Newborns: Differential Diagnosis of Neonatal Sepsis

CARDIAC
Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)
Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN

GASTROINTESTINAL
Necrotizing enterocolitis
Spontaneous gastrointestinal perforation
Midgut volvulus
Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)

HEMATOLOGIC
Neonatal purpura fulminans
Immune-mediated thrombocytopenia
Immune-mediated neutropenia
Severe anemia
Malignancies (congenital leukemia)
Langerhans cell histiocytosis
Hereditary clotting disorders
Familial hemophagocytic lymphohistiocytosis

METABOLIC
Hypoglycemia
Adrenal disorders: adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia
Inborn errors of metabolism: organic acidurias, lactic acidoses, urea cycle disorders, galactosemia

NEUROLOGIC
Intracranial hemorrhage: spontaneous, caused by child abuse
Hypoxic-ischemic encephalopathy
Neonatal seizures
Infant botulism

RESPIRATORY
Respiratory distress syndrome
Aspiration pneumonia: amniotic fluid, meconium, or gastric contents
Lung hypoplasia
Tracheoesophageal fistula
Transient tachypnea of the newborn

Table 148.7 Definitions of Systemic Inflammatory Respiratory Response Syndrome (SIRS) and Sepsis in Pediatric Patients

SIRS: The systemic inflammatory response to a variety of clinical insults, manifested by two or more of the following conditions:
Temperature instability <35°C (95°F) or >38.5°C (101.3°F)
Respiratory dysfunction:
  Tachypnea >2 SD above the mean for age
  Hypoxemia (Pa_{O_2} <70 mm Hg on room air)
Cardiac dysfunction:
  Tachycardia >2 SD above the mean for age
  Delayed capillary refill >3 sec
  Hypotension >2 SD below the mean for age
Perfusion abnormalities:
  Oliguria (urine output <0.5 mL/kg/hr)
  Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)
  Altered mental status
Sepsis: The systemic inflammatory response to an infectious process

SD, Standard deviation.
From Adams-Chapman I, Stoll BJ. Systemic inflammatory response syndrome. *Semin Pediatr Infect Dis.* 2001;12:5–16.

Temperature Instability

Fever or hypothermia may be the only initial manifestation of serious infection in newborns. However, only approximately 50% of infected newborn infants have a temperature >37.8°C (see Chapter 220). Fever in newborn infants does not always signify infection; it may be caused

by increased ambient temperature, isolette or radiant warmer malfunction, dehydration, CNS disorders, hyperthyroidism, familial dysautonomia, or ectodermal dysplasia. A single temperature elevation is infrequently associated with infection; sustained fever is more likely to be caused by infection. Most febrile infected infants have additional signs compatible with infection, although a focus of infection is not always apparent. Acute febrile illnesses occurring later in the neonatal period may be caused by urinary tract infection, meningitis, pneumonia, osteomyelitis, or gastroenteritis and viral infections (enteroviruses, others) in addition to sepsis, thus underscoring the importance of a diagnostic evaluation that includes blood culture, urine culture, lumbar puncture (LP), and other studies as indicated. Numerous pathogens may cause these late infections (see Table 148.2), including HSV, enteroviruses, respiratory syncytial virus, and bacterial organisms. In premature infants, hypothermia or temperature instability requiring increasing ambient (isolette, warmer) temperatures is more likely to accompany infection.

Respiratory and Cardiovascular Symptoms

Early signs and symptoms of pneumonia may be nonspecific, including poor feeding, lethargy, irritability, cyanosis, temperature instability, and the overall impression that the infant is not well. Respiratory symptoms of increasing severity include grunting, tachypnea, retractions, nasal flaring, cyanosis, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be *superimposed* on RDS or bronchopulmonary dysplasia (BPD). For mechanically ventilated infants, the need to increase ventilator support may indicate infection. Although a common finding in neonatal sepsis, tachycardia is nonspecific. Bradycardia may also occur. Poor perfusion and hypotension are more sensitive indicators of sepsis but tend to be late findings. In a prospective national surveillance study, 40% of neonates with sepsis required volume expansion, and 29% required vasopressor support.

Signs of pneumonia on physical examination, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate. Radiographs of the chest may reveal new infiltrates or an effusion, but if the neonate has underlying RDS or BPD, it is very difficult to determine whether the radiographic changes represent a new process or worsening of the underlying disease.

The progression of neonatal pneumonia can be variable. Fulminant infection is most frequently associated with pyogenic organisms such as GBS (see Chapter 230). Onset may occur during the first hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. With early-onset pneumonia in premature infants, the clinical course and chest radiographs may be indistinguishable from those with severe RDS, particularly for GBS pneumonia.

In contrast to the rapid progression of pneumonia caused by pyogenic organisms, an indolent course may be seen in nonbacterial infection. The onset can be preceded by upper respiratory tract symptoms or conjunctivitis. The infant may demonstrate a nonproductive cough, and the degree of respiratory compromise is variable. Fever is usually absent or low grade, and radiographic examination of the chest shows focal or diffuse interstitial pneumonitis or hyperinflation. Infection can be caused by *C. trachomatis,* CMV, *Ureaplasma urealyticum,* and other respiratory viruses. Rhinovirus has been reported to cause severe respiratory compromise in infants, particularly those who are preterm.

Conjunctivitis

Conjunctival infection is relatively common and may be caused by a variety of organisms. The presentation includes periorbital swelling, conjunctival injection, and purulent conjunctival drainage. *C. trachomatis* and *Neisseria gonorrhoeae* are common causes; other gram-positive and gram-negative organisms are occasionally involved. *Pseudomonas aeruginosa* is an important pathogen in hospitalized preterm infants and may be a precursor to invasive disease. Viral infections (e.g., HSV, adenovirus) are occasionally seen. Recognition of HSV infection is important to prevent corneal injury and dissemination to systemic sites.

Skin and Soft Tissue Infection

Cutaneous manifestations of infection include omphalitis, cellulitis, mastitis, and subcutaneous abscesses. Pustules likely indicate the presence of staphylococcal infection but must be distinguished from the vesicular rash of HSV infection. Staphylococcal pustulosis results in larger, pus-filled lesions often scattered around the umbilicus, whereas HSV infection often appears as tiny vesicles in crops, often on the scalp. The presence of small, salmon-pink papules suggests *L. monocytogenes* infection. Mucocutaneous lesions suggest *Candida* spp. (see Chapter 280.1). Petechiae and purpura may be the result of systemic viral or bacterial infection. Neonatal **mastitis** is caused by *S. aureus* and in an otherwise well appearing afebrile neonate is a localized infection.

Omphalitis

Omphalitis is a neonatal infection resulting from unhygienic care of the umbilical cord, which continues to be a problem, particularly in developing countries. The umbilical stump is colonized by bacteria from the maternal genital tract and the environment (see Chapter 144). The necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. Omphalitis may remain a localized infection or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, and the liver. Abdominal wall cellulitis or necrotizing fasciitis, with associated sepsis and a high mortality rate, may develop in infants with omphalitis. Prompt diagnosis and treatment are necessary to avoid serious complications. *S. aureus* and gram-negative organisms are common involved pathogens.

Tetanus

Neonatal tetanus remains a serious infection in resource-limited countries (see Chapter 257). It results from unclean delivery and unhygienic management of the umbilical cord in an infant born to a mother who has not been immunized against tetanus. The surveillance case definition of neonatal tetanus requires the ability of a newborn to suck at birth and for the first few days of life, followed by an inability to suck. Neonatal tetanus typically occurs in infants 5-7 days after birth (range: 3-24 days) and is complicated by difficulty swallowing, spasms, stiffness, seizures, and death. Bronchopneumonia, presumably resulting from aspiration, is another complication and cause of death. Neonatal tetanus can be prevented by immunizing mothers before or during pregnancy and by ensuring a clean delivery, sterile cutting of the umbilical cord, and proper cord care after birth.

LABORATORY FINDINGS

Maternal history and infant signs should guide diagnostic evaluation (Table 148.8). Additionally, signs of systemic infection in newborn infants may be unrevealing, so laboratory investigation plays a particularly important role in diagnosis. Cultures and cell counts are obtained from blood and urine. Cerebrospinal fluid (CSF) should be sent for Gram stain, routine culture, cell count with differential, and protein/glucose concentrations. Surface swabs, blood, and CSF are often obtained for HSV testing. Except for culture and directed pathogen testing, no single laboratory test is completely reliable for diagnosis of invasive infection in the newborn. CBC may demonstrate elevated or decreased WBC count, often with a shift toward more immature forms. Thrombocytopenia can be seen in systemic bacterial, fungal, or viral infection. Hyponatremia, acidosis, and other electrolyte abnormalities can be seen. Hyperbilirubinemia is nonspecific but may be an indication of systemic infection, particularly of the urine tract. Elevated serum transaminases may be a clue to systemic HSV, enterovirus, or other viral infection.

Various **serum biomarkers** have been investigated for their ability to identify infants with serious bacterial infection (SBI). An immature-to-total phagocyte count (I/T ratio) (≥0.2) has the best sensitivity of the neutrophil indices for predicting neonatal sepsis. After the newborn period, serum C-reactive protein (CRP), procalcitonin, and ferritin have demonstrated reasonable sensitivity and specificity for SBI.

Table 148.8 Evaluation of a Newborn for Infection or Sepsis

HISTORY (SPECIFIC RISK FACTORS)
Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy):
- Urinary tract infection
- Chorioamnionitis
- Maternal colonization with group B *Streptococci*, *Neisseria gonorrhoeae*, herpes simplex
- Low gestational age/birthweight
- Multiple birth
- Duration of membrane rupture
- Complicated delivery
- Fetal tachycardia (distress)
- Age at onset (in utero, birth, early postnatal, late)
- Location at onset (hospital, community)

Medical intervention:
- Vascular access
- Endotracheal intubation
- Parenteral nutrition
- Surgery

EVIDENCE OF OTHER DISEASES*
Congenital malformations (heart disease, neural tube defect)
Respiratory tract disease (respiratory distress syndrome, aspiration)
Necrotizing enterocolitis
Metabolic disease (e.g., galactosemia)

EVIDENCE OF FOCAL OR SYSTEMIC DISEASE
General appearance, neurologic status
Abnormal vital signs
Organ system disease
Feeding, stools, urine output, extremity movement

LABORATORY STUDIES
Evidence of Infection
Culture from a normally sterile site (blood, CSF, other)
Demonstration of a microorganism in tissue or fluid
Molecular detection (blood, urine, CSF) by specific PCR and/or 16S ribosomal DNA
Maternal or neonatal serology (syphilis, toxoplasmosis)

Evidence of Inflammation
Leukocytosis, increased immature/total neutrophil count ratio
Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate, procalcitonin, ferritin
Cytokines: interleukin-6, interleukin-B, tumor necrosis factor
Pleocytosis in CSF or synovial or pleural fluid
Disseminated intravascular coagulation: fibrin degradation products, D-dimer

Evidence of Multiorgan System Disease
Metabolic acidosis: pH, P_{CO_2}
Pulmonary function: P_{O_2}, P_{CO_2}
Renal function: blood urea nitrogen, creatinine
Hepatic injury/function: bilirubin, alanine transaminase, aspartate transaminase, ammonia, prothrombin time, partial thromboplastin time
Bone marrow function: neutropenia, anemia, thrombocytopenia

*Diseases that increase the risk of infection or may overlap with signs of sepsis.
CSF, Cerebrospinal fluid; PCR, polymerase chain reaction.

CRP may be monitored serially in newborn infants to assess response to therapy. Their value in the initial diagnosis of sepsis in the newborn period has yet to be clarified. The American Academy of Pediatrics (AAP) Committee on the Fetus and Newborn reiterated in a 2018 early-onset sepsis guideline update that lab tests alone should not be used to diagnose sepsis. Cytokines (both proinflammatory cytokines such as interleukin [IL]-6 and tumor necrosis factor-α and antiinflammatory cytokines such as IL-4 and IL-10), chemokines, and other biomarkers are increased in infected infants.

Tables 148.8 and 148.9 list clinical features and laboratory parameters that are useful in the diagnosis of neonatal infection or sepsis.

GENERAL APPROACH TO MANAGEMENT

In the absence of specific signs of focal infection, therapy for presumed infection in the neonate is often empirical and initiated on the basis of fever or hypothermia, listlessness, irritability, or apneic episodes. Antibiotics are chosen to cover the organisms typically causing neonatal sepsis, including GBS, gram-negative organisms, *Listeria*, and *Enterococcus*. Because the latter two organisms are intrinsically resistant to cephalosporins, ampicillin is generally included in the empirical treatment of infants with presumed neonatal infection (Table 148.10). Initiation of antibiotics within 1 hour of onset is recommended and has a survival advantage.

An empirical regimen for suspected **early-onset infection** in a term or late preterm infant includes ampicillin and gentamicin. This has long been a standard regimen for early-onset sepsis and provides coverage for the most prevalent organisms, predominantly GBS and *E. coli*. Resistance of *E. coli* to ampicillin or gentamicin has been reported; approximately 1 in 10 isolates are resistant to both ampicillin and gentamicin. Ampicillin plus cefotaxime (if available) or cefepime may be substituted if the patient presents with infection after discharge from the nursery, or when infection with resistant *E. coli* is suspected. Ceftriaxone is typically not used in the neonatal period due to precipitation with intravenous calcium and displacement of bound bilirubin causing hyperbilirubinemia. There is concern that cephalosporins may be associated with higher rates of mortality in neonates compared to ampicillin and gentamicin. Alterations to the standard regimen may be appropriate in some circumstances, such as for critically ill newborns, with illness out of proportion to degree of prematurity, at highest risk of infection given maternal risk factors and delivery characteristics.

HSV infection may present without cutaneous signs, in the absence of maternal history of infection, and in mothers receiving suppressive antiviral therapy. Therefore management of the ill newborn requires a high index of suspicion for HSV infection. Surface swabs, blood, and CSF are obtained for HSV culture or polymerase chain reaction (PCR), and empirical acyclovir is often recommended while the results of these studies are pending (see Chapters 220 and 299).

Systemic infection caused by *Candida* spp. is a concern in hospitalized infants, particularly extremely preterm infants with central venous access catheters and prior antibiotic and steroid exposure. Empirical therapy for fungal infection may be indicated for those at highest risk, as well as those with specific clinical signs such as erythematous rash, thrombocytopenia, hyperglycemia, and invasive devices.

Definitive therapy is based on identification and susceptibility of the offending organism. In almost all circumstances, the *narrowest* antibiotic with activity against the organism is chosen. Duration of therapy depends on the organism and the site of infection. In neonates with culture-proven sepsis, the usual course of therapy is typically 7-10 days. Longer treatment courses may be warranted if a specific focus of infection is identified (e.g., meningitis, osteomyelitis, septic arthritis). Antimicrobial therapy should be altered based on the susceptibility profile of the pathogen isolated. In infants with a negative blood culture but a clinical status that remains concerning for a systemic inflammation, other etiologies and potential focal sources of infection should be investigated. Sepsis is unlikely in these infants if appropriately obtained blood cultures are sterile by 48 hours.

PREVENTION

Intrapartum antibiotics are used to reduce vertical transmission of GBS (Table 148.11), as well as to lessen neonatal morbidity associated with preterm labor and preterm premature rupture of membranes (see Chapter 230). With introduction of selective intrapartum antibiotic prophylaxis to prevent perinatal transmission of GBS, rates of early-onset neonatal GBS infection in the United States declined from 1.7/1,000 live births to 0.25/1,000. Intrapartum chemoprophylaxis does *not* reduce the rates of late-onset GBS disease and has no effect on the rates of infection with non-GBS pathogens. Of concern is a possible increase in gram-negative infections (especially *E. coli*) despite a reduction in early GBS sepsis by intrapartum antibiotics.

Table 148.9 Culture-Based and Non–Culture-Based Diagnostics for Neonatal Sepsis

CATEGORY	PARAMETER	OPTIMAL TIMING, VOLUME OF SPECIMEN, ROUTINE/INVESTIGATIONAL*	APPLICABILITY FOR NEONATAL SEPSIS
CULTURE BASED			
Blood	Culture	>1 mL of whole blood, from two sites	Gold standard for bacteremia
CSF	Culture	When clinically feasible	Gold standard for bacterial meningitis
Urine	Culture	>72 hr of life	Not useful for EOS; indicated for LOS evaluation
Tracheal aspirate	Culture	Neonates with endotracheal tube in place and signs of progressive respiratory distress	Usually reflects colonization
NON–CULTURE BASED			
Neutrophil indices	Neutropenia Absolute neutrophil count Absolute immature neutrophil count	After 12 hr of life Consider GA, delivery mode, altitude, arterial versus venous sampling, time since birth	Neutropenia better predictor for sepsis than leukocytosis
Neutrophil markers	CD64	Elevated for 24 hr after infection Requires 50 μL blood Results within hours Investigational	Cut points between 2.38 and 3.62 optimal sensitivity, specificity, and NPV for EOS
Platelet count	Thrombocytopenia and thrombocytosis	Late findings; slow to respond	Thrombocytopenia associated with fungal infection
CSF cell count	CSF WBC	Uninfected neonates: mean 10 cells/mm^3; range up to 20 cells/mm^3	Does not predict culture-proven meningitis
CSF chemistries	CSF protein CSF glucose	Term <100 mg/dL Preterm higher; 70–80% of serum glucose	Elevated in fungal meningitis Low glucose specific for bacterial meningitis
Acute phase reactants	CRP Procalcitonin	8-24 hr after infection 2-12 hr after infection	Good NPV Better sensitivity but less specificity than CRP

**Investigational* refers to an assay or parameter that is undergoing evaluation for clinical use and applicability.
CSF, Cerebrospinal fluid; EOS, early-onset sepsis; GA, gestational age; LOS, late-onset sepsis; MHC II, major histocompatibility complex class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.
From Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *Am J Perinatol.* 2013;30(2):131–141.

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS and early-onset GBS disease is significantly reduced by selective intrapartum chemoprophylaxis (see Fig. 230.4) but does still occur. Neonatal infection with *Chlamydia* can be prevented by identification and treatment of infected pregnant women (see Chapter 272). Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, by cesarean delivery before rupture of membranes, and by antiretroviral treatment of the infant after birth (see Chapter 322).

Prevention of congenital and perinatal infections predominantly focuses on maternal health. The Centers for Disease Control and Prevention (CDC) recommends the following screening tests and treatment when indicated:

1. All pregnant women should be offered voluntary and confidential HIV testing at the first prenatal visit, as early in pregnancy as possible. HIV screening should be part of routine prenatal testing, unless the mother declines testing (opt-out screening). For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use, HIV-infected partners), repeat testing in the third trimester is recommended. Rapid HIV screening is indicated for any women who presents in labor with an undocumented HIV status, unless she declines testing.
2. A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit. Repeat screenings early in the third trimester and again at delivery are recommended for women in whom syphilis test results in the first trimester were positive and for those at high risk for infection during pregnancy. Infants should not be discharged from the hospital unless the syphilis status of the mother has been determined at least once during pregnancy and preferably again at delivery.
3. Serologic testing for hepatitis B surface antigen (HBsAg) should be performed at the first prenatal visit, even if the woman has been previously vaccinated or tested. Women who were not screened prenatally, those who are at high risk for infection (multiple sexual partners, intravenous drug use, HBsAg-positive sex partner), and those with clinical hepatitis should be retested at the time of delivery.
4. A maternal genital culture for *C. trachomatis* should be performed at the first prenatal visit. Young women (<25 years) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the third trimester.
5. A maternal culture for *N. gonorrhoeae* should be performed at the first prenatal visit. Those at high risk for infection should be retested in the third trimester.
6. All pregnant women at high risk for hepatitis C infection (intravenous drug use, blood transfusion or organ transplantation before 1992) should be screened for hepatitis C antibodies at the first prenatal visit.
7. Evidence does not support routine testing for bacterial vaginosis in pregnancy. For asymptomatic women at high risk for preterm delivery, testing may be considered. Symptomatic women should be tested and treated.
8. The CDC recommends universal screening for vaginorectal GBS colonization of all pregnant women at 36 0/7 and 37 6/7 weeks of gestation and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS (see Table 148.11) (see Figs. 230.2 and 230.3).

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Table 148.10 Management and Prevention of Neonatal Sepsis

CONDITION	THERAPY	ADDITIONAL CONSIDERATIONS
EMPIRICAL MANAGEMENT		
Early-onset sepsis	Ampicillin + aminoglycoside 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections	• Consider a third-generation cephalosporin or carbapenem for meningitis or severe illness with high suspicion for gram-negative infection • Tailor therapy to pathogen • Should discontinue empiric therapy if pathogen not isolated
Late-onset sepsis	Vancomycin or antistaphylococcal penicillin (i.e., nafcillin, oxacillin) + aminoglycoside Duration dependent on pathogen and site	• Gram-positive coverage should be based on local epidemiology, MRSA colonization, CONS risk factors, and clinical presentation • Aminoglycoside-based regimen preferred to cephalosporin given reduced risk of resistance • Consider cephalosporin if meningitis suspected • Consider a carbapenem if third-generation cephalosporin recently received • Consider amphotericin for fungal etiologies • Tailor therapy to pathogen • Consider discontinuation of therapy if pathogen not isolated
NONANTIMICROBIAL TREATMENT STRATEGIES		
Recombinant G-CSF Recombinant GM-CSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections
IVIG	Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis
PREVENTION STRATEGIES		
IAP	Administration of penicillin or ampicillin 4 hr before parturition	Successfully reduces rates of EOS caused by GBS No effect on LOS GBS
Fluconazole prophylaxis	Administration of weight-based dosing to neonates <1,500 g	Most beneficial in NICUs with high baseline rates of invasive candidiasis
BLF supplementation with a probiotic, *Lactobacillus rhamnosus* (GG)	BLF is a human milk glycoprotein with a role in innate immune response LGG enhances the activity of lactoferrin	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT Additional confirmatory studies warranted

BLF, Bovine lactoferrin supplementation; CONS, coagulase-negative staphylococci; EOS, early-onset sepsis; GBS, group B *Streptococcus*; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin, LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; RCTs, randomized controlled trials; VLBW, very low birthweight.
Data from Carr R, Modi N, Doré C. G-CSF and GM-CSF for treating or preventing neonatal infections. *Cochrane Database Syst Rev*. 2003;(3):CD003066. Brocklehurst P, Farrell B, King A, et al. INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin. *N Engl J Med*. 2011;365:1201–1211. Manzoni P, Decembrino L, Stolfi I, et al. Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology: Lactoferrin and prevention of late-onset sepsis in the pre-term neonates. *Early Hum Dev*. 2010;86(Suppl 1):59–61.
From Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *Am J Perinatol*. 2013;30(2):131–141.

Table 148.11 Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset Group B *Streptococcus* Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F)† Intrapartum NAAT‡ positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Chapter 230.
†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.
‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 wk gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C/100.4°F) is present, intrapartum antibiotic prophylaxis is indicated.
GBS, Group B streptococcus; NAAT, nucleic acid amplification test.
From Verani J, McGee L, Schrag S. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59(RR-10):1–36.

Chapter 149

Congenital and Perinatal Infections

Sallie R. Permar and Emma L. Mohr

Infections are a frequent and important cause of neonatal morbidity and mortality. **Congenital** or **intrauterine** infections (i.e., those transmitted across the placenta) and **perinatal** infections (i.e., those transmitted from the mother to the fetus or newborn infant during the birth process) represent two major routes of neonatal infection.

149.1 Congenital Infections

Sallie R. Permar and Emma L. Mohr

In utero infections are caused by a variety of etiologic agents, including bacteria, viruses, fungi, and protozoa. Clinical manifestations of congenital infectious diseases in neonates can range from asymptomatic or subclinical to life-threatening disease. History and physical examination findings, in addition to laboratory testing and/or radiologic imaging, provide insight into the best approach for prevention and treatment of congenital infectious diseases in this immunologically immature population (see Fig. 148.2 and Table 148.2).

GENERAL APPROACH

Prenatal counseling on methods to prevent congenital infections is the best approach for improving infant outcomes. Once a fetus or infant is suspected of having a congenital or perinatal infection, infectious as well as noninfectious processes, such as underlying congenital heart disease, genetic disorders, and inborn errors of metabolism, should be considered in the differential diagnosis. Because maternal infection is a prerequisite for infection in the fetus, a thorough history is essential to assess the mother for her symptoms, travel, diet, medication use, occupational exposures, and any **sexually transmitted infections (STIs)** during pregnancy. Clinical manifestations are varied and overlap for many of the pathogens causing intrauterine infection. Laboratory testing and/or radiologic imaging is often required to confirm the diagnosis. Treatment depends on the specific pathogen and can range from symptomatic management with close follow-up for long-term sequelae to targeted antimicrobial therapy.

PATHOGENESIS

The route and timing of infection can provide helpful clues as to the potential infectious etiology (Fig. 149.1 and Table 149.1). First-trimester infection may alter embryogenesis and result in malformations of the heart and eyes, as seen in congenital rubella syndrome. Third-trimester infection (e.g., congenital toxoplasmosis) can result in active infection with signs of hepatomegaly, splenomegaly, and generalized lymphadenopathy at birth. Infections that occur late in gestation (e.g., congenital syphilis) may lead to a delay in clinical manifestations until weeks to years after birth.

Intrauterine infection from cytomegalovirus (CMV), *Treponema pallidum*, *Toxoplasma gondii*, rubella virus, varicella-zoster virus (VZV), and human parvovirus B19 may cause minimal or no symptoms in the mother but still may be transmitted across the placenta to the fetus. The presence of maternal antibodies to rubella prevents maternal infection and congenital transmission, but transmission across the placenta of CMV can occur despite preexisting immunity, albeit at a lower rate compared to primary maternal CMV infection. Regardless of the mother's immune status, the placenta may act as a barrier, and the fetus may or may not be infected. If infection occurs, signs may or may not be noted in the fetus during pregnancy. Infection can result in spontaneous abortion, congenital malformation, intrauterine growth restriction (IUGR), premature birth, stillbirth, acute or delayed disease in the neonate, or asymptomatic persistent infection with sequelae later in life.

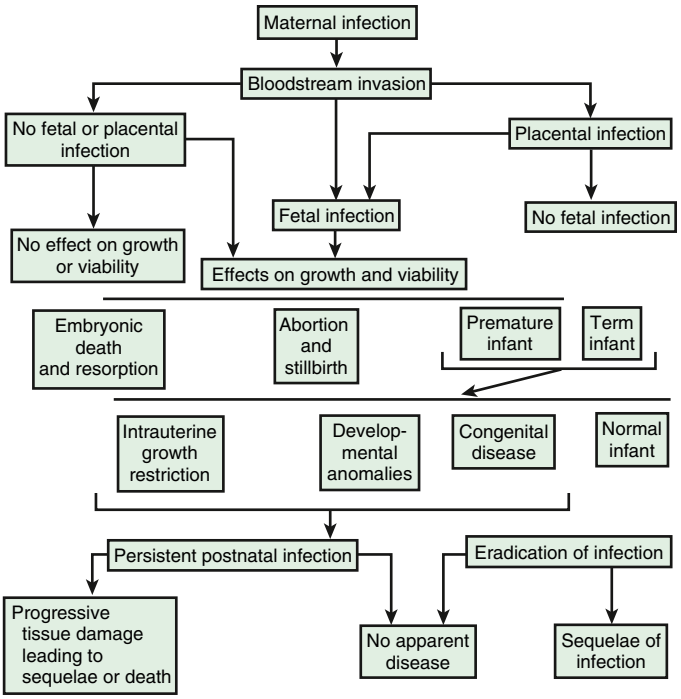

Fig. 149.1 Pathogenesis of hematogenous transplacental infections. (*Adapted from Klein JO, Remington JS. Current concepts of infections of the fetus and newborn infant. In: Remington JS, Klein JO, eds. Infectious Diseases of the Fetus and Newborn Infant, 8th ed. Philadelphia: Saunders; 2002.*)

PREVENTION

Prevention of congenital infections includes behavioral and therapeutic interventions. Counseling-based interventions are effective in reducing CMV infection, but few healthcare providers report counseling their patients on CMV prevention. Counseling on hygienic practices, such as washing hands after diaper changes and avoiding contact with saliva, decreases CMV transmission risk. Safer sex practices, safe food preparation practices, and preventing mosquito bites are some of the recommendations that prevent congenital and perinatal infections. Prenatal and maternal vaccination and control of existing maternal infections are other strategies of preventing congenital infection. Prevention recommendations are presented in Table 149.2.

CLINICAL MANIFESTATIONS

The clinical manifestations of intrauterine infections can range from asymptomatic to severe multiorgan system complications. For some agents (e.g., CMV, *T. pallidum*), ongoing injury after birth can lead to late sequelae as well. The specific clinical signs in the newborn period are usually not sufficient to make a definitive diagnosis but are useful to guide more specific laboratory testing. Symptomatic congenital infections often affect the central nervous system (CNS; brain and eyes) and the reticuloendothelial system (RES; bone marrow, liver, and spleen). Table 149.3 presents the clinical manifestations of some specific congenital infections. Congenital Zika virus infection has features that are rarely seen with other congenital infections (Table 149.4). For example, no hematologic or hepatic laboratory abnormalities have been documented in infants with congenital Zika virus infection. Table 149.5 provides late sequelae of some congenital infections.

Table 149.1 Specific Agents in Effects of Transplacental Fetal Infection on the Fetus and Newborn Infant

	DISEASE				
ORGANISM	**PREMATURITY**	**INTRAUTERINE GROWTH RESTRICTION/LOW BIRTHWEIGHT**	**DEVELOPMENTAL ANOMALIES**	**CONGENITAL DISEASE**	**PERSISTENT POSTNATAL INFECTION**
Viruses	CMV HSV Rubeola Smallpox HBV HIV* SARS-CoV-2 Zika	CMV Rubella VZV* HIV Zika	CMV Rubella VZV Coxsackievirus B* HIV Zika	CMV Rubella VZV HSV Mumps* Rubeola Vaccinia Smallpox Coxsackievirus B Poliovirus HBV HIV LCV Parvovirus Zika	CMV Rubella VZV HSV HBV HIV Zika
Bacteria	*Treponema pallidum* *Mycobacterium tuberculosis* *Listeria monocytogenes* *Campylobacter fetus* *Salmonella typhi*			*T. pallidum* *M. tuberculosis* *L. monocytogenes* *C. fetus* *S. typhi* *Borrelia burgdorferi*	*T. pallidum* *M. tuberculosis*
Protozoa	*Toxoplasma gondii* *Plasmodium** *Trypanosoma cruzi*	*T. gondii* *Plasmodium* *T. cruzi*		*T. gondii* *Plasmodium* *T. cruzi*	*T. gondii* *Plasmodium*

*Association of effect with infection has been suggested and is under consideration.
CMV, Cytomegalovirus; HBV, hepatitis B virus; HSV, herpes simplex virus; LCV, lymphocytic choriomeningitis virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VZV, varicella-zoster virus.
From Maldonado YA, Nizet V, Klein JO, et al. Current concepts of infections of the fetus and newborn infant. In: Wilson CB, Nizet V, Maldonado Y, et al., eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn*, 8th ed. Philadelphia: Elsevier; 2016. Tables 1–5; and from Woodworth KR, Olsen EO, Neelam V, et al. Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy - SET-NET, 16 Jurisdictions, March 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1635–40.

DIAGNOSIS

During Pregnancy

The presence of IUGR or a physical abnormality on a prenatal fetal ultrasound raises concern for a congenital infection. The well-known acronym **TORCH**—***T****. gondii*, **O**ther (*T. pallidum*, human parvovirus B19, HIV, Zika virus, others), **R**ubella, **C**ytomegalovirus, and **H**erpes simplex virus (HSV)—is a historical mnemonic but is less useful given the number of *other* infections that need to be considered. The routine ordering of TORCH serology panels *is not* recommended because the presence of a pathogen-specific IgG response in the mother indicates past infection but does not establish if the infection occurred during pregnancy. Maternal IgM titers to *specific* pathogens are only moderately sensitive, and a negative result cannot be used to exclude infection. Testing the mother for the pathogen of concern itself, such as testing for CMV, HIV, or Zika viremia, can shed some light onto the potential congenital pathogens of concern.

In certain cases, a fetal blood sample with cordocentesis can be obtained and tested for total and pathogen-specific IgM assays, polymerase chain reaction assays (PCRs), or cultures. A positive *pathogen-specific* IgM test is strongly suggestive of infection, but a negative test does not rule out the organism as the cause of the fetopathy. Amniotic fluid can also be obtained and sent for PCR or culture. The presence of CMV, *T. gondii*, or human parvovirus B19 in amniotic fluid indicates the fetus likely is infected but cannot establish the severity of disease. Although HSV is included in the TORCH acronym, it is rarely isolated from amniotic fluid and is rarely transmitted across the placenta from mother to fetus. Fetal blood can be collected to test for human parvovirus B19 IgM and PCR.

Newborn Infant

When a congenital infection is suspected because clinical signs are present at birth, a complete blood count with differential and platelet count along with measurements of transaminases and total/direct bilirubin are routinely performed. Additional evaluations may include a dilated funduscopic examination for retinopathy, auditory brainstem response (ABR) for those failing the newborn hearing screen, and CNS imaging. If available, pathologic examination of the placenta and/or cord may be informative. Infectious diseases consultation is valuable in guiding the evaluation.

Neonatal antibody titers for specific pathogens are often difficult to interpret because IgG is acquired from the mother by transplacental passage, and a positive result may reflect the mother's past infection and not infection of the newborn. Neonatal IgM antibody titers to specific pathogens have high specificity and only moderate sensitivity; a negative result cannot be used to exclude infection. Paired maternal and fetal-neonatal IgG antibody titers showing higher or rising infant IgG antibodies can diagnose some congenital infections (e.g., syphilis). Total cord blood IgM and IgA are not actively transported across the placenta to the fetus yet are not specific or sensitive enough for intrauterine infection.

PCR testing of infant saliva, urine, and/or blood for CMV and other viral infections is sensitive, specific, and widely accepted over virus cultures, yet should be performed within the first 2 weeks of life to distinguish congenital infection from perinatal or postnatal infection. The Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL; Palo Alto, CA: www.pamf.org/serology/; telephone: (650) 853-4828; e-mail: remingtonlab@sutterhealth.org) offers specialized tests and physician experts to aid in the diagnosis of congenital toxoplasmosis. Testing for Zika virus with real-time reverse-transcription PCR (rRT-PCR) from neonatal urine and serum and IgM enzyme-linked immunosorbent assay (ELISA) from neonatal serum is recommended. However, the most reliable method of testing has not been established. In endemic areas, this workup

Table 149.2 Prevention Strategies for Congenital and Perinatal Infections

PATHOGEN	PREVENTION STRATEGY
CMV	Hygienic education to avoid direct contact with toddler urine/saliva, avoid new sexual partners
HSV	Prevention of maternal STI near delivery and exposure of newborn to active maternal lesions
VZV	Vaccination of nonpregnant women of childbearing age with a negative varicella history or vaccine immunity
Rubella virus	Vaccination of nonpregnant women of childbearing age with no immunization history
HIV	Safe sex practices; maternal treatment with HAART on infection
SARS-CoV-2	Prenatal and maternal vaccination, masking, and social distancing
Zika virus	Prevention of mosquito bites and safe sex practices with persons who have recently traveled to endemic areas
Toxoplasma gondii	Avoiding undercooked meat, avoiding unpasteurized goat milk, avoiding raw mollusks, avoid contact with litter or soil potentially contaminated with cat feces
Treponema pallidum	Safe sex practices; screening in nonpregnant populations

HSV, Herpes simplex virus; CMV, cytomegalovirus; VZV, varicella-zoster virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STI, sexually transmitted infection; HAART, highly active antiretroviral therapy.

From Auriti C, De Rose DU, Santisi A, et al. Pregnancy and viral infections: Mechanisms of fetal damage, diagnosis and prevention of neonatal adverse outcomes from cytomegalovirus to SARS-CoV-2 and Zika virus. *Biochim Biophys Acta Mol Basis Dis.* 2021;1867:1–17; Maldonado YA, Read JS. American Academy of pediatrics committee on infectious diseases: diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. *Pediatrics.* 2017;139(2):e20163860; US Preventive Services Task Force: Screening for syphilis infection in pregnant women, February 2018.

should be done soon after delivery because it is difficult to distinguish congenital from perinatal and postnatal infection if testing is done later.

SPECIFIC INFECTIOUS AGENTS

Important congenital infections include more than the TORCH agents. The following is a list of pathogens that may be transmitted across the placenta and the respective chapters where they are discussed in more detail, including treatment.

Bacteria

Listeria monocytogenes (Chapter 234)
Syphilis *(Treponema pallidum)* (Chapter 264)

Viruses

Cytomegalovirus (Chapter 302)
Hepatitis B (Chapter 406)
Hepatitis C (Chapter 406)
Herpes simplex virus (Chapter 299)
Human immunodeficiency virus (Chapter 322)
Human parvovirus B19 (Chapter 298)
Lymphocytic choriomeningitis virus (Chapter 318)
Rubella (Chapter 294)
Varicella-zoster virus (Chapter 300)
Zika virus (Chapter 314.12)

Parasite

Toxoplasmosis (*Toxoplasma gondii)* (Chapter 336)

149.2 Perinatal Infections

Sallie R. Permar and Emma L. Mohr

Perinatal infections are defined as those that are transmitted from the mother to the fetus or newborn infant during the birth process. Despite recommended universal screening of pregnant women for *Chlamydia trachomatis*, gonorrhea, and group B streptococcus (GBS), transmission to the newborn still occurs. In addition to these STIs, other bacteria, viruses, and *Candida* spp. may cause perinatal infections. Similar to congenital infections, their presentation can range from asymptomatic to a sepsis-like syndrome.

GENERAL APPROACH

The general approach is like that for congenital infections and includes a detailed maternal history and a careful examination of the newborn (see Chapter 148). Many clinical syndromes overlap; therefore laboratory testing is usually required to establish a specific microbiologic etiology and guide management decisions.

PATHOGENESIS

The human birth canal is colonized with aerobic and anaerobic bacteria. **Ascending amniotic infection** may occur with either apparently intact membranes or relatively brief duration of membrane rupture. Infectious agents can also be acquired as the newborn infant passes through the vaginal canal. This acquisition may result in either colonization or disease. Factors influencing which colonized infants will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies.

Chorioamnionitis has been historically used to refer to microbial invasion of the amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane for >18 hours. The term *chorioamnionitis* is confusing because it does not convey the spectrum of inflammatory or infectious diseases, it leaves out other intrauterine components that can be involved (e.g., decidua), and it results in significant variability in clinical practice, with the potential for a significant number of well newborns being exposed to antimicrobial agents. The term **intrauterine inflammation or infection at birth**, abbreviated as **Triple I**, is preferred because of the heterogeneous nature of conditions that can affect the mother and neonate (Table 149.6). Regardless of the definition used, prematurity (<37 weeks) is associated with a greater risk of early-onset sepsis, especially with GBS.

Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

CLINICAL MANIFESTATIONS

Most perinatal infections present clinically during the first month of life. Initial signs and symptoms may be either nonspecific or focal (see Chapter 148). Additional information on specific infectious agents and their management are reviewed in the chapters indicated below.

SPECIFIC INFECTIOUS AGENTS

Bacteria

Chlamydia trachomatis (Chapter 272)
Escherichia coli (Chapter 246)
Genital mycoplasmas (Chapter 270)
Group B streptococci (Chapter 230)
Neisseria gonorrhoeae (Chapter 238)
Syphilis *(Treponema pallidum)* (Chapter 264)

Table 149.3 Clinical Manifestations of Specific Neonatal Infections Acquired in Utero or at Delivery

RUBELLA VIRUS	CYTOMEGALOVIRUS	*TOXOPLASMA GONDII*	HERPES SIMPLEX VIRUS	*TREPONEMA PALLIDUM*	ENTEROVIRUSES	ZIKA VIRUS
Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Adenopathy Hearing deficits Myocarditis Congenital defects* Bone lesions* Glaucoma* Chorioretinitis *or* retinopathy* Cataracts* Microphthalmia	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Microcephaly* Intracranial calcifications* Hearing deficits Chorioretinitis *or* retinopathy Optic atrophy	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus* Microcephaly Maculopapular exanthems Intracranial calcifications* Myocarditis Bone lesions Chorioretinitis *or* retinopathy* Cataracts Optic atrophy Microphthalmia Uveitis Sensorineural hearing loss*	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Microcephaly Maculopapular exanthems Vesicles* Myocarditis Chorioretinitis *or* retinopathy Cataracts Conjunctivitis *or* keratoconjunctivitis*	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Adenopathy Maculopapular exanthems* Bone lesions* Glaucoma Chorioretinitis *or* retinopathy Uveitis	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Adenopathy Maculopapular exanthems Paralysis* Myocarditis* Conjunctivitis Keratoconjunctivitis	Fetal brain disruption sequence* Cortical thinning Ventriculomegaly Microcephaly Microphthalmia *or* coloboma Cataracts Contractures Hearing deficits Epilepsy Hyper/hypotonia

*Has diagnostic significance for this infection.
Adapted from Maldonado YA, Nizet V, Klein JO, et al. Current concepts of infections of the fetus and newborn infant. In: Wilson CB, Nizet V, Maldonado Y, et al., eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn*, 8th ed. Philadelphia: Elsevier; 2016: Tables 1–6; with data from Moore CA, Staples JE, Dobyns WB, et al. Characterizing the pattern of anomalies in congenital zika syndrome for pediatric clinicians. *JAMA Pediatr.* 2017;171(3):288–295.

Table 149.4 Syndromes in the Neonate Caused by Congenital Infections

ORGANISM	SIGNS
Toxoplasma gondii	Hydrocephalus, diffuse intracranial calcification, chorioretinitis
Rubella virus	Cardiac defects, sensorineural hearing loss, cataracts, microcephaly, "blueberry muffin" skin lesions, hepatomegaly, interstitial pneumonitis, myocarditis, disturbances in bone growth, intrauterine growth restriction
CMV	Microcephaly, periventricular calcifications, jaundice, petechiae or purpura, hepatosplenomegaly, intrauterine growth restriction, sensorineural hearing loss
HSV	Skin vesicles or scarring, eye scarring, microcephaly or hydranencephaly, vesicular skin rash, keratoconjunctivitis, meningoencephalitis, sepsis with hepatic failure
Treponema pallidum	Bullous, macular, or eczematous skin lesions involving palms and soles; rhinorrhea; dactylitis and other signs of osteochondritis and periostitis; hepatosplenomegaly; lymphadenopathy
VZV	Limb hypoplasia, cicatricial skin lesions, ocular abnormalities, cortical atrophy
Parvovirus B19	Nonimmune hydrops fetalis
HIV	Severe thrush, failure to thrive, recurrent bacterial infections, calcification of basal ganglia
Zika virus	Microcephaly, lissencephaly, cerebellar hypoplasia, akinesia syndrome, macular scarring, retinal mottling, subcortical calcifications, hypertonia

HSV, Herpes simplex virus; CMV, cytomegalovirus; VZV, varicella-zoster virus.
From Maldonado YA, Nizet V, Klein JO, et al. Current concepts of infections of the fetus and newborn infant. In Wilson CB, Nizet V, Maldonado Y, et al., eds. *Remington and Klein's Infectious Diseases of the Fetus and Newborn*, 8th ed. Philadelphia: Elsevier; 2016: Tables 1–7.

Table 149.5 Late Sequelae of Intrauterine Infections

	INFECTION				
CLINICAL SIGN	CMV	RUBELLA VIRUS	*TOXOPLASMA GONDII*	*TREPONEMA PALLIDUM*	ZIKA VIRUS
Hearing loss	+	+	+	+	+
Dental/skeletal problems	(–)	+	(–)	+	+
Developmental delays	+	+	+	+	+
Seizures	+	+	+	+	+

+, Present; (–), rare or absent; CMV, cytomegalovirus.

Table 149.6 Classification of Triple I and Isolated Maternal Fever

TERMINOLOGY	FEATURES
Isolated maternal fever	Maternal oral temperature ≥39°C is considered a "documented fever" If the oral temperature is ≥38°C but ≤39°C, repeat the measurement in 30 min If the repeat value is ≥38°C, it is considered a "documented fever"
Suspected Triple I	Fever without a clear source with *any* of the following: 1. Baseline fetal tachycardia (>160 beats/min for 10 min) 2. Maternal WBC >15,000/mm^3 in the absence of corticosteroids 3. Purulent fluid from the cervical os
Confirmed Triple I	All the above (from suspected Triple I) with *any* of the following: 1. Amniocentesis-proven infection through positive Gram stain 2. Low glucose of amniotic fluid or positive amniotic fluid culture 3. Placental pathology consistent with infection

Triple I, Intrauterine inflammation or infection at birth; WBC, white blood cell count.
Adapted from Higgins RD, Saade G; Chorioamnionitis Workshop participants: Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. *Obstet Gynecol* 2016;127(3):426–436.

Table 149.7 Laboratory Tests in the Diagnosis of Specific Perinatal Infections

INFECTIOUS AGENT	ACCEPTABLE SPECIMEN(S) FROM INFANT UNLESS OTHERWISE INDICATED	LABORATORY TEST
Chlamydia trachomatis	Conjunctiva, nasopharyngeal swab, tracheal aspirate	DFA or culture using special transport media NAATs are not FDA-approved for specimens from neonates*
Genital mycoplasmas (*Mycoplasma hominis, M. genitalium, Ureaplasma urealyticum*)	Tracheal aspirate, blood, CSF	Culture using special transport media NAATs
Neisseria gonorrhoeae	Conjunctiva, blood, CSF, synovial fluid	Finding gram-negative intracellular diplococci on Gram stain is suggestive Culture on special media establishes the diagnosis
Syphilis *(Treponema pallidum)*	Serum (mother)	A nontreponemal test (RPR or VDRL) and if reactive, a specific treponemal test† or reverse-sequence screening: specific treponemal test and if reactive, a quantitative nontreponemal test
	Serum	RPR/VDRL
	CSF	VDRL
Cytomegalovirus	Urine, saliva (with confirmational urine), blood, or CSF (if CNS involvement)	CMV DNA PCR Obtained within 3 wk of birth
Enteroviruses	Blood, nasopharyngeal swab, throat swab, conjunctival swab, tracheal aspirate, urine, stool, rectal swab, vesicle fluid, CSF	PCR Cell culture (sensitivity depends on serotype and cell lines used)
Hepatitis B	Serum (mother) Serum	HBsAg If mother's HBsAg is positive, at age 9 mo, test the infant for HBsAg and hepatitis B surface antibody
Herpes simplex viruses 1 and 2	Conjunctiva, skin vesicle scraping, whole blood, mouth vesicles	PCR or cell culture
	CSF	PCR
	"Surface cultures" (mouth, nasopharynx, conjunctiva, and anus)	PCR or cell culture
HIV	Serum (mother) Whole blood (infant)	Fourth-generation HIV antigen/antibody test HIV DNA PCR (performed on peripheral blood mononuclear cells) or RNA PCR (performed on plasma)
Candida species	Blood, skin biopsy, or CSF	Culture
Zika virus	Blood, urine	RNA PCR Also assay CSF for RNA if obtained for other reasons
	Blood	IgM antibodies Also assay CSF for IgM if obtained for other reasons
SARS-CoV-2	Nasopharynx, oropharynx, nose, saliva, trachea	RT-PCR or direct antigen testing

*Published evaluations of NAATs for these indications are limited, but sensitivity and specificity is expected to be at least as high as those for culture.
†Treponemal tests include the *T. pallidum* particle agglutination (TP-PA) test, *T. pallidum* enzyme immunoassay (TP-EIA), *T. pallidum* chemiluminescent assay (TP-CIA), and fluorescent treponemal antibody absorption (FTA-ABS) test.
DFA, Direct immunofluorescence assay; NAAT, Nucleic acid amplification test; FDA, U.S. Food and Drug Administration; CSF, Cerebrospinal fluid; VDRL, Venereal Disease Research Laboratories; RPR, rapid plasma reagin; HBsAg, hepatitis B surface antigen; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse-transcription polymerase chain reaction.
Created with data from pathogen-specific chapters within Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Redbook: 2021-2024 Report of the Committee on Infectious Diseases*, 32nd ed. Itasca, IL: American Academy of Pediatrics; 2018; p. 729–744.

Viruses

Cytomegalovirus (Chapter 302)
Enteroviruses (Chapter 297)
Hepatitis B (Chapter 406)
Herpes simplex virus (Chapter 299)
Human immunodeficiency virus (Chapter 322)
Severe acute respiratory syndrome coronavirus 2 (Chapter 311)

Fungi

Candida spp. (Chapter 280)

DIAGNOSIS

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, chorioamnionitis). STIs acquired by a pregnant woman, including syphilis, *N. gonorrhoeae*, and *C. trachomatis,* have the potential for perinatal transmission.

Neonates with perinatal infections often present with nonspecific symptoms and signs; therefore the general diagnostic evaluation for the ill neonate as discussed in Chapter 202 should be followed. Table 149.7 provides a summary of laboratory tests that are useful to diagnose specific perinatal infections.

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