Complications of the Late Preterm Infant

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One of the goals of Healthy People 2010 (set in 1998) was to reduce preterm birthrates from 11.6% to 7.6%. However, in 2004, the preterm birthrate of 12.5% was actually higher than the rate in 1998. Approximately 65% of this increase in prematurity rate is attributed to the increasing birthrate of the late preterm infant. Care of the late preterm infant is far more complicated than many hospital policies and clinical guidelines imply. It cannot be stressed enough to frontline clinicians that late preterm infants are not full-term infants. Their care should not be defined by the same policies and practices that govern term infants. The purpose of this article is to explore the complications that accompany late preterm birth. The following complications will be discussed: thermoregulation challenges, feeding difficulty, late neonatal sepsis, prolonged physiologic jaundice, hypoglycemia, possible neurodevelopmental differences, and respiratory problems. Key words: complications, late preterm infant, near-term infant

Short gestation/low birth weight is the leading cause of neonatal mortality in the United States. Infants are defined as premature when birth takes place before 37 completed weeks' gestation (259 days from the first day of the mother's last menstrual period). According to the March of Dimes, more than 4 million live births occur in the United States each year and preterm births account for nearly half a million of those births. According to the National Center for Health Statistics, most of this increase in premature births is due to increases in the birthrates of moderately preterm infants (32–36 weeks).

When looking at the birthrate of premature infants by gestational age, the very preterm infant (<32 weeks) birthrate has stayed relatively constant during the past 2 decades, ranging from 1.8% to 2.0%, whereas late preterm infants (34–36 weeks) comprise the fastest growing population and account for greater than 70% of all preterm births and 8.5% of all births in the United States (Fig 1). In addition, over the past 15 years there has been a shift toward earlier gestation in the distribution of singleton live births, largely due to the increase in births occurring between 34 and 39 weeks' gestation and the significant decrease in births occurring after 40 weeks. The mean birth gestational age among spontaneous births changed significantly from 1992 to 2002 from 39.2 weeks to 38.9 weeks (P < .0001, Fig 2). It is widely recognized that preterm birth places newborns at increased risk for morbidity and mortality compared with their term counterparts, especially for the very low-birth-weight infants; however, the fastest growing subgroup of this population known as the “late preterm infant” continues to be underappreciated in terms of newborn risk.

A 2005 invitational workshop of medical and nursing experts entitled “Optimizing Care and Outcome of the Near-Term Pregnancy and the Near-Term Newborn Infant” and conducted by the National Institute of Child Health and Human Development took on the task of defining this group. At the conclusion of the workshop, late preterm infants were classified as those newborn infants born between 34 completed weeks (34 0/7 weeks or day 239) and less than 37 completed weeks (36 6/7 weeks or day 259) of gestation. Late preterm has taken the place of the “near-term infant” so as to convey the concept that this subgroup is indeed premature and not almost term.
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While survival rates for late preterm newborns are higher compared with those born at earlier gestations, a 2000 *JAMA* study showed that at the population level, the etiologic fraction can be considerable. In the United States and Canada, 6.8% to 8.0% of all infant deaths were attributed to being born between 34 and 36 weeks’ gestation. In addition, studies have shown a high rate of readmission to the hospital when these infants were discharged within 48 hours of birth.

There are a plethora of unique needs and complications that accompany the late preterm newborn infant. The physiologic limitations of a late preterm newborn that contribute to increased risk and greater incidence of morbidity when compared with a term infant include feeding difficulty, body temperature instability, late neonatal sepsis, prolonged physiologic jaundice, hypoglycemia, possible neurodevelopmental differences, and respiratory problems because of immaturity (Fig 3). Despite these complications, late preterm newborns are often clinically treated and discharged on the same timetable as their term counterparts.

In addition to being at risk for increased morbidity and mortality, the care of late preterm newborns has significant economic implications. According to estimates by the Institute of Medicine, the economic burden caused by all preterm births in the United States in 2005 was at minimum $26.2 billion or $51,600 per preterm infant. The intensity of care required by more immature newborns results in greater per infant costs, while the great numbers of late preterm newborns contribute to overall costs for preterm infant

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**Figure 1.** Gestational age distribution of singleton preterm births, United States, 2002 ($N = 394,996$). Adapted with permission from Davidoff et al.6(p9)

**Figure 2.** Shifting distribution of gestational age among spontaneous singleton live births, United States, 1992, 1997, and 2002. Adapted with permission from Davidoff et al.6(9)
care. In 1996, a population-based study in California concluded that preventing late preterm infant births could have saved $49.9 million.13

It is apparent that more research regarding the healthcare of late preterm infants is needed. The purpose of this article was to explore the complications that accompany late preterm birth. The following complications will be discussed: thermoregulation challenges, feeding difficulty, late neonatal sepsis, prolonged physiologic jaundice, hypoglycemia, possible neurodevelopmental differences, and respiratory problems.

THERMOREGULATION AND HYPOGLYCEMIA

When birth occurs before glycogen stores have been sufficiently developed, the newborn infant lacks adequate sources of energy for homeostasis, including both thermoregulation and glucose homeostasis. Two key factors in the survival of preterm newborn infants are prevention of heat loss and promotion of thermal stability.14 It has been well documented in the literature that newborns are predisposed to cold stress at birth unless preventative measures are taken.15,16 The normal thermoregulatory response of neonates to cold stress includes increased involuntary activity, vasoconstriction, and nonshivering thermogenesis.14

Cold stress in preterm newborn infants is of greater concern because of an immature epidermal barrier, a higher ratio of surface area to birth weight than in term infants, and more frequent delivery room interventions increasing their risk of hypothermia.17 Furthermore, mechanisms for increasing metabolism for heat, including increasing the use of glucose and glyco-
gen stores, have not fully developed.18 Additional factors that place a preterm newborn at high risk include decreased brown fat, greater body water content, immature metabolic mechanisms for responding to thermal stress, and delayed development of skin blood-flow control reducing the ability to maintain heat by peripheral vasoconstriction.19

The need for thermal management is often appreciated in the very preterm infants but overlooked in the late preterm population.14,20,21 Hypothermia increases the metabolic demands on an infant who is already stressed.22 Recognizing that hypothermia in this population may not be due to prematurity but may be due to infection or hypoglycemia makes measuring and interpreting the data correctly an important task for nurses. The ultimate goal of thermoregulation is to maintain a neutral thermal environment, that is, the ambient temperature within which the infant can maintain normal body temperature with minimum metabolic rate and oxygen consumption.23 Hypothermia is a risk factor for infant mortality and inhibits growth. The decrease in body temperature accelerates the metabolic rate and stimulates thermogenesis or heat production.

Understanding the balance between what causes heat loss and what causes heat gain is a primary concept that both nurses and parents must understand in caring for these infants. When preparing for discharge, parents must learn about maintaining an adequate environmental temperature and assessing their infant. A neutral thermal body temperature for the late preterm infant is defined as 97.7°F to 99.5°F.21 Parents must understand the need to appropriately dress their infant and be aware of the risk for hypothermia. Discharge teaching about how to take an infant temperature and guidelines regarding when to call the pediatric provider should be priority teaching points for families.

As mentioned above, cold stress can lead to and worsen hypoglycemia in this age group. Lack of glycogen stores coupled with rapid depletion of glucose from increased metabolic demands can result in hypoglycemia in late preterm newborns. While it is recognized that hypoglycemia can have detrimental effects, the actual level at which these effects occur remains undefined. All hospitals have a protocol to meet the national standard of care for detection and management of hypoglycemia in the at-risk newborn. Late preterm newborns are at higher risk of hypoglycemia compared with those born at term.24 Insufficient glycogen stores as well as inadequate intake contributes to a higher incidence of hypoglycemia in the late preterm infant than in the full term infant. More importantly, the compensatory
mechanisms responsible for protecting the brain from hypoglycemic injury are not completely developed, placing even greater risk for the late preterm infant. Detecting hypoglycemia requires astute monitoring and an understanding of the clinical signs associated with decreased circulating glucose levels. Increased attention must be paid to late preterms who have been resuscitated as they are at even greater risk for developing hypoglycemia. Diligent monitoring and recognizing the signs of low blood glucose levels enable the nurse to intervene in a timely manner. The signs associated with hypoglycemia include changes in level of consciousness (irritability, excessive crying, lethargy, and/or stupor), apnea, poor feeding, tachypnea, tachycardia, hypotonia, and jitteriness. Hypoglycemia is another potential complication that impacts care for the late preterm newborn and another reason for vigilant monitoring of this preterm infant subpopulation.

INFECTION

Neonatal infection rates vary by both geographic location and within hospitals and nurseries. Preterm birth is the primary risk factor for newborn bacterial infection. Late preterm infants have increased susceptibility to infection because of immune system immaturity, leading to decreased phagocytic cellular defenses and decreased ability to fight infections. In addition, preterm birth leads to decreased transmission of maternal antibodies and thus decreases maternally acquired passive immunity. The neonatal intensive care unit (NICU) setting also places late preterm newborns at risk for nosocomial infections.

Overall, the incidence of neonatal bacterial infection is estimated to be about 1 to 8 newborns per every 1000 live births. Up to 30% of newborns admitted to NICUs have blood cultures positive for microorganisms and even more are diagnosed with clinical infection despite not having positive results of blood cultures.

Generally, there are 3 types of presentation for neonatal bacterial infections:
1. Congenital infections—infected acquired before delivery
2. Early onset—delivery through 72 hours of life
3. Late onset—acquired in the hospital and presenting after 72 hours of life

The timing and clinical presentation of these infections are critical components to appropriate treatment as they differ in epidemiology, pathogenesis, and prognosis (Table 1).

<table>
<thead>
<tr>
<th>Congenital infections</th>
<th>Early onset</th>
<th>Late onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma gondii</td>
<td>Streptococcus</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Listeria monocytogenes</td>
<td>Staphylococcus epidermidis</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Escherichia coli</td>
<td>Pseudomonas</td>
</tr>
<tr>
<td>Herpesvirus</td>
<td>Group B Streptococcus</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>HIV</td>
<td>Candida</td>
<td>Enterobacter family</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td></td>
<td></td>
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<tr>
<td>Treponema pallidum</td>
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</tbody>
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Congenital infections are acquired before delivery or in the intrapartum period. The most common infections stem from Toxoplasma gondii, rubella virus, cytomegalovirus, herpes virus, HIV, parvovirus B19, and Treponema pallidum. Disease severity is dependent on the time of infection during the pregnancy. Risks of transmission of some of these infections are dependent on mode of delivery, time of membrane rupture, and in HIV, maternal viral load.

Early-onset sepsis occurs in the first few days of life and is typically caused by perinatally acquired infections. Early-onset infection is typically caused by microorganisms found in the maternal genital tract. These include Streptococcus, Listeria monocytogenes, Escherichia coli, as well as group B Streptococcus, and Candida. Mortality for early-onset infection is as high as 5% to 50%. Risk factors that increase sepsis development include preterm delivery, prolonged rupture of membranes (greater than 18 hours), maternal fever, and chorioamnionitis.

Late-onset infection occurs after 72 hours of life and often after 5 days of life. The presentation of late-onset infection is often slower with a more focal site. In addition to the organisms in early-onset sepsis, late-onset infection is also caused by Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas, Klebsiella, and Enterobacter. The mortality for late-onset infection is 2% to 6%; however, it is often more challenging to treat because of the resistant strains of the organisms responsible for late-onset sepsis.

Most epidemiologic studies of infection are conducted on very low-birth-weight infants. There are limited recent multicenter data for the late preterm...
infant. We know, however, that the late preterm newborn is examined for possible sepsis 3 times more frequently than term newborns (36.7% vs 12.6%; odds ratio 3.97). In addition, 30% of these late preterm newborns receive antibiotic therapy for 7 days.

Neonatal infection remains a significant cause of morbidity and mortality in the late preterm newborn. Careful evaluation of the clinical signs associated with neonatal infection (Table 2) will decrease the risk of systemic sepsis and the complications associated with infection. Accurate history of these infants including maternal and perinatal assessment is imperative. Prompt antibiotic therapy and diligent infection control practices by each member of the healthcare team are necessary for optimal health of these infants.

**Table 2.** Common signs and symptoms in neonatal infection

<table>
<thead>
<tr>
<th>Respiratory distress</th>
<th>Apnea, tachypnea, grunting, retracting, flaring, cyanosis, hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding abnormalities</td>
<td>Poor feeding, increased residuals, vomiting, projectile vomiting, distention, diarrhea, gastrointestinal bleeding</td>
</tr>
<tr>
<td>Cardiovascular changes</td>
<td>Temperature instability, tachycardia, bradycardia, hyper/hypotension, poor perfusion, decreased urine output</td>
</tr>
<tr>
<td>Neurological changes</td>
<td>Lethargy, irritability, seizures</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Increase in conjugated or unconjugated bilirubin</td>
</tr>
<tr>
<td>Metabolic changes</td>
<td>Metabolic/respiratory acidosis, hypo/hyperglycemia</td>
</tr>
</tbody>
</table>

Jaundice in the late preterm infant results from an increased bilirubin load due to increased bilirubin production and/or decreased bilirubin elimination. Hyperbilirubinemia is the most common cause for hospital readmission during the first week of postnatal life. While for the majority of patients, this condition is transitional and generally benign, high levels of total serum bilirubin can have neurotoxic effects. There is a strong correlation between decreasing gestational age and increasing risk for significant hyperbilirubinemia. The late preterm infant remains relatively immature compared with the term infant in his or her ability to handle unconjugated bilirubin. In the late preterm infant, neonatal hyperbilirubinemia is more prevalent and more pronounced than in the term infant. The late preterm infant has a relatively later peak of serum bilirubin at 5 to 7 days and a tendency to persist similar to that observed in the very low-birth-weight newborn. Late preterm infants are 2.4 times more likely to develop significant hyperbilirubinemia than those of 38 to 42 weeks’ gestation.

One problem regarding late preterm newborns is that they are often cared for in environments in which they are expected to be like term infants. That is, they are cared for in a normal newborn nursery and often thought to be as mature as their term counterparts. The practice of discharging these infants as healthy term infants before 72 hours of life increases the potential incidence for bilirubin-induced neurologic dysfunction. In fact, late preterm infants are represented disproportionately in the US Pilot Kernicterus Registry. Preterm infants, discharged as healthy, account for a disproportionate readmission rate to hospitals for the management of jaundice and hyperbilirubinemia.

Avoiding the development of marked hyperbilirubinemia and reducing the risk of acute bilirubin encephalopathy and kernicterus in the late preterm infant require preventative care and screening tools. Significant clinician education in newborn nurseries, parental education, and timely postdischarge follow-up and treatment when clinically indicated are critical in these neonates. Shortened hospital length of stay (LOS) (<48 hours after delivery) is not recommended for late preterm infants. The American Academy of Pediatrics recommends close discharge follow-up to identify infants at risk and initiate treatment. Counseling parents on when to call their pediatric clinician is another preventative strategy.

It is imperative that clinicians remain concerned about high levels of bilirubin, defined by its peak, rate of rise, duration, and binding ability to albumin. Preventative and safe treatment are key in reducing hospitalizations for severe hyperbilirubinemia and kernicterus.

**RESPIRATORY DISTRESS**

Respiratory distress is defined as sustained distress for more than 2 hours after birth accompanied by grunting, flaring, tachypnea, retractions, or supplemental oxygen requirement. The incidence of respiratory issues increases as gestational age is decreased, and the rate of respiratory distress dramatically increases in infants born at less than 37 weeks. Respiratory distress was observed more often in late preterm neonates (28.9% vs 4.2%) than in term newborns (Fig 3). Even more staggering is that neonates born at 35 weeks are 9 times more likely to have respiratory distress compared with infants born at 38 to 40 weeks’ gestation.
The last few weeks of gestation prepare the fetus for success in the transition from uterine life. For effective gas exchange to occur, alveolar spaces must be cleared of excess fluid and ventilated, and pulmonary blood flow must be increased to match ventilation and perfusion. From 34 0/7 to 36 6/7 weeks' gestation, terminal respiratory units of the lung evolve from alveolar saccules to mature alveoli lined with type 1 epithelial cells. During this period, pulmonary capillaries begin to bulge into the space of each terminal sac and sufficient surfactant is attained. The production of surfactant, which begins at 32 weeks' gestation, decreases the risk of respiratory distress syndrome. The lungs, while functional, are not yet mature in the late preterm period. The last 6 weeks of gestation is when the fetus begins to develop synchrony and control over breathing; this maturation decreases the risk of apnea of prematurity.

Late preterm neonates suffer from a higher incidence of transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension, and respiratory failure than do term infants. Most of these infants who develop transient respiratory distress recover without any long-term consequences; however, a significant number progress to respiratory distress syndrome. The production of surfactant, which begins at 32 weeks' gestation, decreases the risk of respiratory distress syndrome. The lungs, while functional, are not yet mature in the late preterm period. The last 6 weeks of gestation is when the fetus begins to develop synchrony and control over breathing; this maturation decreases the risk of apnea of prematurity.

FEEDING PROBLEMS

Feeding the late preterm infant presents a challenge to care providers, as the infant may not be able to fully coordinate the suck-swallow-breathe pattern. Immature muscle tone and neurologic processes necessary to maintain the airway and effective sucking patterns for oral feeding have not developed in these infants. At 34 weeks' gestation, the overall brain weight is only 65% of term weight. In addition, 50% of the increase in cortical volume occurs between 34 and 40 weeks' gestation.

There is a paucity of evidence regarding the neurodevelopmental outcomes of late preterm infants at school age. The available data regarding outcomes for preterm infants come from the large body of literature surrounding the extremely low-birth-weight infant. Data regarding the developmental outcome of the late preterm infant is scarce. Recently, Morse and colleagues reported that late preterm infants are more likely to have a diagnosis of developmental delay within the first 3 years of life, are more likely to be referred for special needs preschool resources, and are more likely to have problems with school readiness compared with their term counterparts.

Late preterm infants comprise a vulnerable population in need of careful monitoring for neurologic outcomes. It is imperative to improve our understanding of maturation and brain development in the later weeks of gestation. Increased expenditures for developmental aberrations, learning difficulties, and delays have implications for high costs to school districts and society. Research is needed regarding long-term outcomes of this cohort and therapeutic interventions including early intervention services to help guide clinical protocols and help clinicians advocate for more strategies to increase public support for this subgroup of the premature population.

NEURODEVELOPMENT

Neurodevelopmental abnormalities in more preterm (<34 gestational weeks) infants are well recognized, and there is new evidence to suggest that neurologic morbidity is also a problem of the late preterm infant. The late preterm newborn's brain weight is a fraction of the full-term newborn's brain weight. A significant proportion of brain growth and development occurs in the last 6 weeks of gestation. Much of the development in the cortical gray matter, white matter, and cerebellum happens during this time. At 34 weeks' gestation, the overall brain weight is only 65% of term weight. In addition, 50% of the increase in cortical volume occurs between 34 and 40 weeks' gestation.
Furthermore, breast-feeding provides an even greater challenge with greater risk for inadequate nutrition particularly if discharge occurs prior to the mother’s milk coming in and successful feeding establishment. These infants have fewer awake periods, less stamina, and generally do a poor job of stimulating and emptying the breast, often resulting in poor milk production. Poor feeding places these infants at risk for breast-feeding failure with additional potential for dehydration and delayed discharge. Many times, milk supply is not established prior to discharge of infants in well-baby nurseries, and when coupled with the late preterm infant’s inability to stimulate supply, these infants are at high risk for readmission.

There is little research to show appropriate guidelines for feeding these infants. Generally, the late preterm infant is fed on the basis of hospital protocol or prescribers’ orders. There are few hospitals that feed these infants on the basis of their feeding cues. One guideline available is breast-feeding the near-term infant (35–37 weeks’ gestation) provided by The Academy of Breastfeeding Medicine. Parents must be counseled on what cues their infants will give and when to wake their infant up to feed him/her if the infant is sleepy. Furthermore, establishing how much intake their infant will require and what kind of assistance a breast-feeding mother may need should be determined prior to discharge. Close interaction with the lactation team to help determine milk supply and transfer will ensure better hydration and weight gain for these infants. Breast-fed infants should be seen by their healthcare provider 48 hours after discharge and visiting nursing services should be offered as a resource, if possible. This education and resource utilization will make for proper hydration and weight gain for the late preterm infant. The establishment of feeding guidelines is one of the most imperative projects that can come out of the current research being done.

CONCLUSION/IMPLICATIONS

One of the goals of Healthy People 2010 (set in 1998) was to reduce preterm birthrates from 11.6% to 7.6%. However, in 2004, the preterm birthrate of 12.5% was actually higher than the rate in 1998. Approximately 65% of this increase in prematurity rate is attributed to the increasing rate of the late preterm infant (8.8% in the United States). Furthermore, results from a 2004 study showed that 66% of late preterm infants were discharged 4 or more days after birth, which is defined as a late discharge. The late preterm group had higher birth hospitalization costs ($26,054) than did full-term infants group ($2087) and also had 3 times the medical costs throughout the first year of life ($12,247 vs $4,069 for the 2 groups, respectively).

Late preterm infants have been termed The Great Imposter. Their size and shape make them appear deceptively innocent and much like a full-term infant. Indeed, their physiologic complications may or may not manifest until 48 to 72 hours of life, and in many cases, these complications do not manifest until they have already been discharged from the hospital. Late preterm infants have a rehospitalization rate that is twice the rate of late preterm infant rate. (8.8% as compared with 17.7%). Furthermore, hospital readmission rates are 2- to 3-fold higher than full-term infants’ rates.

Beyond the human experience of prematurity, there is a greater public health impact. Hospital costs including increased LOS, frequency of complications, and medical outcomes all need to be accounted for in discussing the medical complications and implications of the late preterm infant. A California study noted that the mean LOS and mean cost for a 34-week infant was 5.9 days and $7200, respectively. Furthermore, the authors noted that the mean LOS and cost for a 35-week infant was 3.9 days and $4200. A delay of delivery by 1 week in this age group decreased hospital costs by 42%. This trend continues as gestational age increases, the mean LOS and cost for a 38-week (term) infant was 1.8 days and $1100.

In 2005, the Association of Women’s Health, Obstetric and Neonatal Nurses announced an initiative in collaboration with Johnson & Johnson to improve healthcare and guidelines for this vulnerable population. These guidelines will enable new protocols and pathways to be designed to fit the needs of the late preterm infant in a variety of hospital settings from well-baby nurseries to level III NICUs.

Care of the late preterm infant is far more complicated than many hospital policies and clinical guidelines imply. It cannot be stressed enough to frontline clinicians that late preterm infants are not full-term infants. Their care should not be defined by the same policies and practices that govern term infants. The late preterm infant poses a distinct challenge to both nursing and medical providers as important differences in clinical care and outcomes become apparent. An understanding of the pathophysiology that accompanies a late preterm birth will enable care providers to appropriately act on the signs and symptoms of distress in these neonates. Further educational tools and research will help care providers identify morbidities in the late preterm neonate and advocate for appropriate clinical care for this subgroup of premature infants.
REFERENCES


