Clinical Issues in the Management of Late Preterm Infants

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Abstract

Prematurity is defined as birth before 37 weeks of gestation and is the major determinant of morbidity and mortality in newborns. The gestational ages known as near term or late preterm represent about 75% of preterm births and are the fastest growing subgroups of premature infants. These infants range in gestational age from 34 0/7 to 36 6/7 weeks and are at greater risk of morbidity, such as respiratory complications, temperature instability, hypoglycemia, kernicterus, feeding problems, neonatal intensive care unit admissions, and adverse neurological sequelae when compared with term infants. Long-term neurological and school-age outcomes of late preterm infants are concerns of major public health importance because even a minor increase in the rate of neurological disability and scholastic failure in this group can have a huge impact on the health care and educational systems. There is an urgent need to educate health care providers and parents about the vulnerability of late preterm infants, who are in need of diligent monitoring and care during the initial hospital stay and a comprehensive follow-up plan for post neonatal and long-term evaluations. Clinicians involved in the day-to-day care of late preterm infants, as well as those developing guidelines and recommendations, would benefit from having a clear understanding of the potential differences in risks faced by these infants, compared with their more mature counterparts.

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Introduction

Prematurity, defined as birth before 37 weeks of gestation, is a major determinant of morbidity and mortality in newborn infants. As the modern era of newborn intensive care evolves, neonatologists have become increasingly focused on improving the care and outcomes for ever smaller and more premature neonates. However, in recent years, a subset of premature neonates born between 34 and 37 weeks gestational age has become the subject of increasing interest.[1] Because these infants represent more than 75% of the total number of preterm infants, their deaths constitute a much larger "etiologic fraction" of neonatal mortality than do those who are more premature. In the USA and Canada, these infants have contributed substantially to overall infant and neonatal mortality, although their mortality rate was significantly lower than that of newborns whose gestational age was less than 33 weeks.[2] In the year 2004, the infant mortality rate among late preterm infants was 3 times higher than among the term infants (7.3 vs 2.4 infant deaths per 1000 live births).[2] Others have pointed out that short-term morbidity, as reflected by increased hypoglycemia, jaundice, apnea, respiratory distress, longer lengths of stay, and higher healthcare costs, is also much greater for this cohort of infants.[3] The question often arises immediately after birth as to the appropriate level of care for infants in this age category, with some receiving care in the neonatal intensive care unit (NICU) and others being cared for in the newborn nursery. The ability to monitor for subtle feeding issues and hypoglycemia, nutritional practices, and discharge feeding plans can vary between the NICU and the newborn nursery, even within the same hospital.

Some experts have suggested that the traditional designation of "near-term" for this group of infants be replaced by the terminology "late preterm" to emphasize that it is preferable for clinicians to approach these babies as premature infants.[4] The unique physiological

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and developmental needs of these late preterm infants are yet to be fully understood. Clinicians involved in the day-to-day care of late preterm infants, as well as those developing guidelines and recommendations, would benefit from a clear understanding of the potential differences in risks faced by these infants when compared with their more mature counterparts.

Definitions

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG) define a premature infant as one who is born before the end of the 37th week of pregnancy, counting from the first day of the last menstrual period.[5] However, there is no consensus on the definition of preterm neonates born between 34 and 37 weeks of gestational age and these infants are often referred to as "near-term neonates." A National Institute of Child Health and Human Development workshop in 2005 suggested designating neonates born between 34 0/7 weeks and 36 6/7 weeks as "late preterm" neonates.[4] This panel was of the opinion that by redefining this cohort of neonates as "late preterm," greater attention to the special needs of this group would be identified,[6-7] resulting in more diligent evaluation, monitoring, and follow-up by healthcare providers. This definition of late preterm also conveys an impression that this group of neonates is still premature, not almost term, as the near-term definition may imply.

National Institute of Child Health and Human Development workshop in 2005 suggested designating neonates born between 34 0/7 weeks through 36 6/7 weeks as "late preterm" neonates.

Epidemiology

Rates of prematurity have steadily increased over the past decade.[8] There are multiple reasons for this, including demographic transformations, changes in infertility treatments, increasing mean age of childbearing mothers, and increasing incidence of multiple gestation pregnancies.[9-11] In the year 2006, approximately 1 in 8 newborns in the USA were born prematurely, representing 542,893 births and 12.8% of all live births.[8] However, 75% of these early births, or about 9% of total USA births in 2006, were late preterm infants, born between 34 and 37 weeks of gestation[8] (Fig 1).

FIG 1. Incidence of late preterm births: USA, 1996-2006. In 2006, there were 387,791 late preterm births, representing 9.1% of all live births. (Reprinted with permission from the National Center for Health Statistics, final natality data. Retrieved from http://www.marchofdimes.com/peristats January 20, 2010.)

Late preterm newborns are the fastest growing subset of babies.[1] The factors that have contributed most significantly to the recent increased incidence of late premature births include the increasing proportion of women choosing to have babies later in life,[12] increased demand for assisted reproductive technology, and increased incidence of multiple gestation pregnancies.[13,14] In addition, the increased incidence may also be partially attributable to the ever-increasing rates of childbirth interventions, especially Caesarean section.[15]

Maternal Age and Race as a Risk Factor for Prematurity

Maternal age is a risk factor for preterm birth, with higher preterm birth rates found among both younger and older groups of mothers in USA. During the period from 2004 to 2006, late preterm birth rates were highest for women ages 40 and older (11.8%) followed by women under the age of 20 years (10%)[8,16] (Fig 2). Furthermore, a steady increase in pregnant mothers in these 2 high risk age groups has been noted. Of all infants born during the period of 2004-

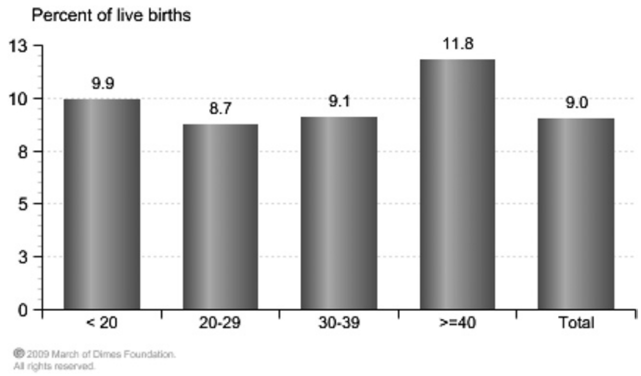

FIG 2. Late preterm birth by maternal age: USA, 2004-2006. Maternal age is a risk factor for late preterm birth, with higher premature birth rate found among the younger and older mothers in the USA. (Reprinted with permission from the National Center for Health Statistics, final natality data. Retrieved from http://www.marchofdimes.com/peristats January 20, 2010.)

2006, almost 10% were born to mothers under the age of 20 years and 3% were born to mothers aged 40 years and older, a significant change from previous years.[8]

Maternal race and ethnicity also appear to play a role in preterm infant birth rates.[17] Preterm birth rates have been found to be 1.5 times higher in non-Hispanic black mothers when compared with Hispanic and non-Hispanic white mothers. During the years 2004-2006 in the USA, late preterm birth rates were highest for Black infants (11.5%), followed by Native Americans (10%), whites (8.6%), and Asians (7.9%).[8,17]

Factors significantly contributing to the increased incidence of late preterm neonates are increased demand for assisted reproductive technology, increased incidence of multiple gestation pregnancies, and increased incidence of Caesarian births.

Artificial Reproductive Technology (ART) and Preterm Births

Since 1996, there has been a 3-fold increase in USA in the incidence of women successfully delivering a viable baby following infertility treatment. ART is associated with an increased likelihood of multiple gestations. Indeed, 2002 national data revealed that 16% of all twins and 44% of infants born in triplets or high-order multiples were conceived with assisted conception.[14] As multiple gestation pregnancies have an increased risk of preterm birth, increasing use of ART is linked to the increasing preterm rates overall and to late preterm birth rates in particular.[14,18]

Multiple Gestation and Late Preterm Births

There has been an epidemic of multiple gestations observed in the last 2 decades, primarily attributed to 2 concomitant modern trends: the older parturient population because of delayed child-bearing age and a rise in the use of infertility therapies. Multiple pregnancies present numerous, unique challenges in obstetrical diagnosis and management. Of all the live births in the USA in 2006, 3.4% were multiple births.[8] Multiple births, when compared with singleton births, were almost 5 times more likely to result in the birth of a late preterm neonate[8] (Fig 3). Additionally, in the USA the mean age at delivery for twins was 35.3 weeks, 32.2 weeks for triplets, and 29.9 weeks for quadruplets compared with 38.8 weeks for singletons.[19] Although the offspring of a multiple gestation may be born earlier than singletons, preterm twin and triplet neonates appear to have similar birth weight, morbidity, and mortality as singleton controls of the same gestational age.[20,21]

Most twins and many high-order multiples deliver in the late preterm period because of either spontaneous preterm labor or iatrogenic interventions intended to treat maternal and fetal medical complications. Expectant mothers of multiples are almost 6 times more likely to be hospitalized for obstetrical complications, such as preterm labor, premature rupture of membranes, intrauterine growth restriction, placental abruption, and maternal hypertensive disease.[22] ACOG's current practice guidelines regarding multiples suggest that pregnancy can be continued normally in the presence of normal fetal growth and volumes, reassuring antenatal testing and absence of maternal complications. Nonetheless, many multiple births occur in the late preterm period, either by spontaneous preterm births or by elective late preterm delivery.[22] Numerous strategies have been employed to prevent spontaneous late premature births

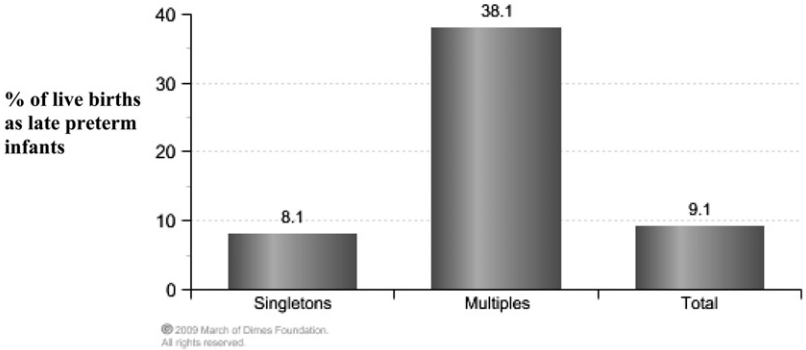

FIG 3. Late preterm by plurality: USA, 2006. Compared with singleton births in the USA in 2006, multiple births were almost 5 times as likely to be late preterm infants. (Reprinted with permission from the National Center for Health Statistics, final natality data. Retrieved from http://www.marchofdimes.com/peristats January 20, 2010.)

in this cohort of the population, including prophylactic cervical cerclage placement,[23,24] prophylactic bed rest,[25] prophylactic administration of various tocolytic agents,[26,27] and home monitoring of uterine contractions.[28] However, none of these practices have been found to be successful in preventing preterm deliveries in this population. Currently, there are insufficient data in terms of maternal risks and neonatal benefits to support the use of any of these interventions in women with suspected early labor in the late preterm period.

According to ACOG, management of preterm labor should involve the use of tocolysis and glucocorticoids only up to 34 weeks of gestation and this may have contributed to the increased rate of late preterm births.

Spontaneous Preterm Labor, Caesarean Section, Induction of Labor, and Their Impact on Late Preterm Births

The increasing trend of electively delivering at earlier gestational ages has raised concerns about the impact that this may have on maternal and fetal health. Maintaining a delicate balance between the risks to the fetus and benefits to the mother associated with continuing a pregnancy versus delivering early remains a major obstetrical challenge.

During the past 15 years in the USA, the percentage of infants born before 40 weeks of gestation has increased and the percentage of those born after 40 weeks of gestation have decreased.[1,29] The shift in gestational age at birth raises the risk for the birth of physiologically immature infants who then are at increased risk to develop associated complications of prematurity. More than 7% of deliveries resulting from preterm labor occurred between 34 and 37 weeks gestation, resulting in a 12% increase in births in this gestational age range between 1992 and 2004.[1] Standard obstetrical management of preterm labor and premature prolonged rupture of membranes may influence the percentage of these cases that result in late preterm birth beyond 34 weeks of gestational age. According to the guidelines published by ACOG, the management of preterm labor should involve the use of tocolysis and glucocorticoids only up to 34 weeks of gestation.[30] These practices may have contributed to the increasing rate of late preterm births and the subsequent acute respiratory morbidities.[30] Modification of current management strategies could potentially decrease the incidence of late preterm births and its morbidities. However, additional research is needed to identify the best balance between perinatal and neonatal management.

In the year 2006, 30% of live births were delivered by Caesarean deliveries, leading to an astounding 50% increased rate of Caesarean section in USA in the last decade.[8]

This largely reflects a sharp increase in primary Caesarean section rates, which may further increase subsequent Caesarean rates because of the increased likelihood of repeat Caesarean section in these future pregnancies. Although many Caesarean sections occur for valid indications, there is speculation that many occur electively because of maternal and/or practitioner preference in the absence of medical or obstetrical indications.[31] Although birth records do not allow more precise estimates, published reports estimate that the Caesarean deliveries occurring because of a maternal request account for between 4% and 18% of all Caesarean deliveries in USA.[31] It is often difficult to distinguish between Caesarean deliveries performed electively at maternal request and those performed for medical indications from the medical records alone.[31] Such elective interventions in term pregnancies can potentially increase the proportion of deliveries, resulting in a late preterm infant, because delivery date and gestational age estimation prenatally is an inexact and an imperfect science.[32] Commonly used methods, such as Naegle's rule and second trimester sonograms, are accurate to only within 1 to 2 weeks of the actual gestation age, potentially giving a margin of error that moves an expected term delivery into the late preterm category.[32,33]

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Another factor that potentially contributes to the increase in late preterm birth is the decreasing trend of vaginal birth after a previous Caesarean section and acceptance or standardization of repeat Caesarean deliveries. The vaginal birth after a previous Caesarean section rate rose steadily from 1980 to a high of 28% in 1997 and then fell to a low rate of 10% in 2003.[8,34] This changing trend likely contributed to the increased incidence of iatrogenic late preterm births during this time.[34]

To avoid iatrogenic prematurity and to minimize the morbidity associated with elective induction of labor and elective Caesarean section, ACOG recommends that elective delivery should not be performed before 39 weeks of gestation. In an attempt to further decrease the morbidity associated with elective Caesarean deliveries at term, physicians and patients should be counseled regarding the vulnerability of late preterm infants and the potential for iatrogenic late prematurity morbidity. Furthermore, hospital guidelines should be developed and ensure that elective deliveries are not performed before 39 weeks of gestation age. Additionally, fetal lung maturity should be confirmed when pregnancy dating cannot be established before an elective delivery.

Neonatal Clinical Issues

Recent research focused on late preterm births has revealed that this group of patients experience higher incidences of neonatal complications when compared with their term counterparts. Late preterm infants have a higher risk for respiratory distress syndrome, transient tachypnea of the newborn, hypoglycemia, temperature instability, jaundice, and feeding difficulties.[3,35,36] Recently, McIntyre and Leveno[37] reported that these neonatal morbidities decreased significantly with increasing gestational age between 34 and 39 weeks. Late preterm infants have also been found to require additional resources leading to higher hospital costs secondary to longer lengths of hospital stay and higher rates of admission to NICU. Furthermore, late preterm infants are more likely to be rehospitalized after initial hospital discharge.

It is estimated that 17,000 infants with a gestation age of more than 34 weeks at birth are admitted to the NICU each year in the USA, representing 33% of all NICU admissions. Nearly 50% of infants born at 34 weeks gestation require neonatal intensive care; this number drops to 15% at 35 weeks and 8% at 36 weeks of gestation.[38]

What follows is a discussion of some of the neonatal issues seen in the late premature group of neonate (Table 1).

Pulmonary System

Respiratory morbidities in late preterm infants delivered spontaneously or by elective Caesarean section have been well documented. This diagnosis accounts for a significant number of admissions to the intensive care unit each year.[39,40] Late preterm infants have a higher incidence of transient tachypnea of the newborn, respiratory distress syndrome, pulmonary hypertension, and respiratory failure than term infants.[3,35,36] Decreased clearance of lung fluid and/or relative deficiency of surfactant remain central to the pathophysiology of these disorders. Birth in the absence of labor also contributes to the observed pulmonary dysfunction.[41] There is considerable evidence that physiological events in the last few weeks of pregnancy coupled with the onset of spontaneous labor and

TABLE 1. Late preterm infants and neonatal morbidities

Morbidity	Late preterm vs term infants
Respiratory issues	Higher incidence of transient tachypnea of newborn, respiratory distress syndrome, pulmonary hypertension, and respiratory failure[3,35,36]
Resuscitation at birth	Almost twice the chance of need for any resuscitation at birth[49]
Jaundice	2-4 times likely to develop severe jaundice[5,58,59]
Metabolic	Greater susceptibility to cold stress, more often requires phototherapy for jaundice, more likely to have feeding problems[56,62,65]
Cognitive development	Higher risk for developmental delay and school readiness issues[79]

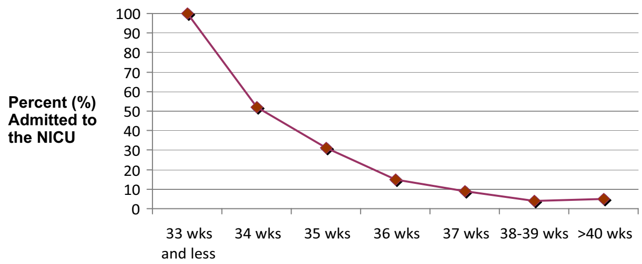

FIG 4. Incidence of NICU admission: late preterm versus term neonates. Graph shows the incidence of admission to the NICU for neonates with a GA above 33 weeks. Almost 50% of all infants born at 34 weeks of GA were admitted to the NICU when compared with less than 10% for neonates more than 37 weeks of GA admitted to the NICU (Source: Bailey S, Hendricks-Munoz K, Mally P. Incidence of respiratory distress syndrome (RDS) among term and late preterm (LPT) neonates. E-PAS 2009:502). (Color version of figure is available online.)

hormonal changes affect the fetus and the mother in ways that result in the rapid maturation and preparation of the fetus for delivery and a smooth neonatal transition. Spontaneous delivery during term gestation is accompanied by a surge in endogenous steroids and catecholamine secretion, which is responsible for some of the pulmonary maturational effects.[41] When delivery occurs during the late premature gestation age, especially by Caesarean section before the onset of labor, the fetus is deprived of these hormonal changes, making the neonatal transition more difficult and increasing the risk of acute respiratory issues in the early neonatal period.[42] This provides partial explanation as to why these infants have a higher incidence of transient tachypnea of the newborn, respiratory distress syndrome resulting from iatrogenic prematurity, persistent pulmonary hypertension with or without hypoxic respiratory failure, each of which also contributes to higher rates of NICU admissions. These late preterm babies admitted to the NICU may potentially require oxygen therapy and ventilatory support, including mechanical ventilation, and have increased rates of acute respiratory morbidity, when compared with the term infants.[43-46]

Late preterm neonates have a higher risk for respiratory morbidities, hypoglycemia, temperature instability, hyperbilirubinemia, and feeding difficulties when compared to their term counterparts.

The authors performed an observational study over a 15-month period between 2006 and 2007, evaluating the incidence of late premature births and associated respiratory morbidities when compared with their term counterparts. Of 5600 total live births at their center during the study period, approximately 10% of all births were late preterm births. Of all neonates born at 34 weeks gestation age, 50% required admission to the NICU. Admission rates to the NICU were also greater in other late preterm groups with 30% of all premature neonates born at 35 weeks and 20% of all premature neonates born at 36 weeks requiring admission to the NICU. This was in stark contrast with a NICU admission rate of less than 10% of all term neonates[47] (Fig 4).

The authors also found that late preterm infants were 8 times more likely to be diagnosed with respiratory distress syndrome, 9 times more likely to be placed on nasal continuous positive pressure ventilation, 5 times more likely to be placed on a ventilator, and 42 times more likely to require surfactant supplementation when compared with the term neonates who were admitted to the NICU during the study period[47] (Table 2).

This study confirms numerous recent reports that late preterm neonates contribute greatly to the overall incidence of respiratory morbidity seen in infants. A study by De Luca et al.[48] revealed a strong age-related trend in respiratory morbidity independent of delivery mode and a 10-fold increase in these morbidities in infants of 34 weeks of gestation age compared with term infants. A retrospective study in Canada by Kitsommart et al.[49] revealed significantly worse respi-

TABLE 2. Risk of respiratory morbidities in late preterm and term neonates

Diagnosis/ Intervention	Late preterm (n = 138)	Term (n = 303)	Odds ratio (95% CI)
RDS	23%	4%	8.0 (3.9-16.5)
TTN	20%	15%	1.3 (0.8-2.2)
Nasal cannula	35%	31%	1.2 (0.8-1.9)
NCPAP	35%	6%	9.0 (4.9-16.4)
Ventilator	13%	3%	4.9 (2.1-11.2)
Surfactant	12%	0.3%	42.2 (5-322)

Respiratory morbidity and respiratory support seen in late preterm versus term infants. RDS = respiratory distress syndrome; TTN = transient tachypnea of newborn; NCPAP = nasal continuous positive pressure ventilation.
Source: Bailey S, Hendricks-Munoz K, Mally P. Incidence of respiratory distress syndrome (RDS) among term and late preterm (LPT) neonates. EPAS 2009:502.

ratory outcomes in 34- to 36-week gestational age infants when compared with term infants; respiratory outcomes included rates of positive pressure ventilation and prevalence of pneumothorax. Others have reported a high incidence of respiratory distress as one of the most common adverse outcomes among late preterm infants.[37,39,40] The implication of these findings is that an overall reduction in respiratory morbidity and possibly other morbidities would likely be seen with a reduction in the overall proportion of late preterm births.

Delivery Room Resuscitation

Late preterm infants should be identified as a high-risk group in need of delivery room attendance for potential resuscitation support because of the above-mentioned risks of immaturity of the physiological systems and in the response to stress factors during labor and birth. The last weeks of pregnancy are critical for complete fetal development and maturation. Biochemical and hormonal modifications associated with spontaneous birth are key factors required for an adequate transition to the extrauterine life.[41] Interruption of pregnancy before the occurrence of these maturational events can hinder the respiratory and hemodynamic transition that normally should take place soon after birth.

de Almedia et al.[50] prospectively evaluated the incidence of bag and mask ventilation in the delivery room for all live-born late preterm and term infants. They found that except for tracheal aspiration for meconium, the chance of needing any resuscitation procedure was approximately 2 times higher in the late preterm group compared with the full-term group. Furthermore, there was a greater proportion of low Apgar scores in the late preterm infants compared with full-term infants.[50]

Gastrointestinal Maturation and Feeding

Much of the neonatal nutrition literature has focused on the management of very low birth infants with little attention to the nutritional management or needs of preterm infants at higher gestation. Nonetheless, the late preterm cohort presents its own nutritional challenges to health care providers.

The gastrointestinal tract continues to develop throughout gestation with tremendous growth and a doubling of intestinal length in the last trimester of pregnancy.[51] This is coupled with a dramatic increase in the surface area largely because of the enormous growth of villi and microvilli during this period.[51] Despite this fact, digestive absorptive capability is usually not a critical problem in late preterm neonates and they adapt quickly to enteral feedings, including the digestion and absorption of lactose, proteins, and lipids.[51-53]

However, there are various aspects of intestinal motor function immaturity that result in feeding intolerance in premature infants. Suck–swallow coordination is not fully developed until the fetus reaches a gestation age of approximately 34 weeks.[54] Motility and gastric emptying can also be delayed.[55] As a consequence, some late preterm infants can require considerably longer time to achieve normal feeding patterns, resulting in prolonged hospital stays.

Deglutition, peristaltic functions, and sphincter control in the esophagus, stomach, and intestines are likely to be less mature in late preterm infants compared with their term counterparts. This may lead to difficulty in coordinating suck and swallowing and a delay in successful breastfeeding with resultant poor weight gain and dehydration during the early postnatal period, potentially increasing the likelihood of rehospitalization.[6,7,56]

The advantages of breastfeeding in premature infants appear to be even greater than those for term infants. However, establishing successful breastfeeding in this group of infants is oftentimes problematic. Because of their immaturity, late preterm neonates may be more sleepy, have less stamina, and have more difficulty with latching on to the mother's breast.[57] These can all be potential barriers for successful breastfeeding. Additionally, mothers who deliver near but not at term are more likely to deliver multiples, or have medical conditions such as diabetes, eclampsia, chorioamnionitis, or a Caesarean section delivery that may also affect the breastfeeding success. Taken together, the maternal and infant problems place the late preterm breastfeeding neonate at increased risk for hypothermia, hypoglycemia, excessive weight loss, slow weight gain, failure to thrive, prolonged artificial milk supplementation, exaggerated jaundice, dehydration, breastfeeding failure, and rehospitalization.[57] These feeding problems are also the most dominant reason for delay in hospital discharges for this cohort of the newborn population.[3]

In summary, although late preterm neonates are born only a few weeks early, they still have a wide spectrum of nutritional needs. The team approach, including input from the nutritionist, occupational therapist, speech pathologist, lactation consultant, and the physician can facilitate choosing successful feeding plans for these infants.

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Hyperbilirubinemia

Hyperbilirubinemia in late preterm neonates is often more prevalent, and when it does occur, it is usually more severe and its course is more protracted than in term neonates. Jaundice in late preterm infants results from an increased bilirubin load due to increased bilirubin production and decreased bilirubin elimination. Moreover, late preterm neonates demonstrate a slower postnatal maturation of hepatic bilirubin uptake and bilirubin conjugation compared with their term counterparts.[58] This exaggerated hepatic immaturity contributes to the greater prevalence, severity, and duration of neonatal jaundice in the late preterm infants.[58,59] Late preterm neonates are vulnerable to developing brain damage because of hyperbilirubinemia and kernicterus.[60] The mechanisms that potentially could account for the increased susceptibility to bilirubin-induced central nervous system injury in late preterm neonates have not been well defined. However, some of the factors that can potentially account for this are the diminished serum bilirubin binding capacity due to the lower serum albumin levels in the late preterm group, an enhanced permeability of the blood–brain barrier to unconjugated bilirubin influx, and an immaturity of neuronal protective mechanism.

Compared with term neonates, late preterm neonates were at an increased risk to develop kernicterus as identified in the USA pilot kernicterus registry and are also at risk for developing signs of bilirubin neurotoxicity at an earlier postnatal age.[61,62]

The immaturity of the suck–swallow mechanism discussed previously can also place late preterm neonates who are breastfed at risk for severe neonatal hyperbilirubinemia.[3] Inadequate breast milk intake, in addition to contributing to a varying degree of dehydration, can enhance hyperbilirubinemia by increasing the enterohepatic circulation of bilirubin and the resultant hepatic bilirubin load. In the context of the exaggerated hepatic immaturity of the late preterm neonate, any further increase in the hepatic bilirubin load will likely result in more marked hyperbilirubinemia.[3]

Pediatricians need to be alert to the potential problems of suboptimal breast milk feeding in late preterm neonates and not be misled by the seemingly satisfactory breastfeeding efforts of these late preterm neonates during their initial stay in the hospital. During this first observed period, limited colostrum volumes make it a challenge to adequately assess the effectiveness of breastfeeding. Ultimately, the best clinical strategy to avoid the development of marked hyperbilirubinemia and the associated risk of bilirubin encephalopathy in late preterm neonate is preventive. It includes nursing and parental education, screening for jaundice in the newborn nursery, the provision of lactation support, timely post discharge follow-up, and appropriate treatment when clinically indicated.

Cold Stress and Hypoglycemia

Despite the increased risk of early neonatal morbidities in the late preterm cohort, pediatricians often presume that the late preterm infant and the term infant are at similar risk for medical problems. Likewise, they generally consider the late preterm infant as a healthy newborn. Demands on limited acute care beds in NICUs, along with established clinical practices, often result in early transition of these infants to the well baby nursery or to the maternity ward to be roomed in with the mother.

Clinicians often consider clinical features of respiratory distress to determine the level of care required for infants after birth and stabilization in the delivery room. Other critical factors required for successful transition during the early hours following birth is the neonate's ability to deal with cold stress and hypoglycemia. These conditions can be easily missed, especially if one does not closely monitor infants in this gestational age group.[63] Cold stress should be of greater concern in both the very preterm infant and the larger late preterm cohort alike and is an important stressor that can potentially hinder a successful transition to the extra uterine environment or precipitate persistence of the fetal circulation or pulmonary hypertension. Late preterm infants are particularly vulnerable to cold stress due to their immature epidermal barrier, a higher ratio of surface area to birth weight than for term infants, and the need for more frequent delivery room interventions. Other factors that can promote heat loss are large temperature gradients between the infant and the ambient temperature of the delivery room, large evaporative heat loss from the wet surface of the newborn, and conductive heat losses to the cooler surfaces on which the infant is placed.[64] Recognition of cold stress following birth especially in late preterm neonates and rapid intervention in the form of prevention strategies are key. Strategies that can help to accomplish a smooth transition include thorough drying of the skin and the scalp with warm blankets, proper skin-to-skin contact with the mother, and swaddling with warm blankets.[64,65]

Late preterm infants are vulnerable to developing brain damage because of hyperbilirubinemia and kernicterus.

Hypoglycemia represents another variable that impacts the level of care needed for the late preterm neonate. It is dangerous to assume that the incidence of hypoglycemia in the late preterm infant is similar to the term neonate. The postnatal decreases in plasma glucose concentration observed in preterm infants is often much greater than that seen in the term infants.[66] This suggests a poor postnatal adaptation that places the late preterm infants at risk of lower serum glucose levels than would be expected in an average term infants.[66] In fact, the incidence of hypoglycemia in preterm infants is 3 times greater than the incidence seen in full-term infants. Furthermore, of those late preterm infants who experience hypoglycemia, nearly two thirds will be in need of dextrose infusions to maintain optimal glucose stability. Although the absolute magnitude of this problem in late preterm neonates is not well documented, it is thought to approach between 10% and 15%.[67,68] The increased risk for hypoglycemia may reflect a delay in hepatic glucose-6-phosphatase activity when compared with their term counterparts. This enzyme catalyzes the terminal step in hepatic glycogenolysis and gluconeogenesis, which represents the primary response to hypoglycemia. In addition, limited enteral intake due to gastrointestinal immaturity and poor suck–swallow coordination also contributes to the risk of hypoglycemia in the late preterm infant. More importantly, the compensatory mechanisms responsible for protecting the brain from hypoglycemic episodes are not yet entirely in place,[69] posing an increased risk of negative neurodevelopmental outcomes. It is important for providers taking care of this cohort of neonates to pay close attention to the anticipation, recognition, diagnosis, and therapy of neonatal hypoglycemia.[69]

Cold stress and hypoglycemia represent components of adaptation that are rarely completed within the delivery room, but rather extend through the first day of life. Irrespective of the mode and place of care—whether in the newborn nursery, rooming in with the mother, or in the intensive care unit, repetitive body temperature and serum glucose measurements are necessary for proper management. Similarly, surveillance for transitional hypoglycemia may extend beyond the first hours following birth due to concomitant cold stress, poor feeding, and/or tachypnea, all of which occur more frequently in late preterm neonates when compared with term infants. A comprehensive understanding of these issues by physicians, nurses, and hospital administrators is essential to determine the resources necessary to care for a cohort of infants in whom the risk of medical problems are often overlooked.[63] (See Table 3 for a sample protocol for

TABLE 3. Sample protocol: "Postnatal transition" monitoring of late preterm infants

- Late preterm infants need closer monitoring in a transitional nursery or neonatal intensive care unit than term infants.
- Feeding: Early initiation of feeds with increased frequency. Trained nursing staff should observe for suck-swallow coordination and reduced endurance and have a lactation consultation within 24 hours of birth.
- Hyperbilirubinemia: Serum testing of bilirubin at 24 hours, visual assessment for jaundice in hospital every 8-12 hours, parental education by the providers to look for worsening jaundice, such as visible yellowing of the skin, inadequate feeding, decreased activity with decreased urine output, and follow-up with pediatrics within 4-5 days.
- Thermoregulation: Axillary temperature should be taken immediately after admission and every 4 hours during their hospital stay. Infant should demonstrate stable temperature at least for 48 hours in a open crib before discharge.
- Close monitoring for signs and symptoms of respiratory distress by the nursing staff in the first 48 hours is important. Parents should be trained to look for signs of respiratory distress, such as nasal flaring, increased retractions, and grunting.

the monitoring of the postnatal transition of late preterm infants.)

Cold stress and hypoglycemia represent components of adaptation that are rarely completed within the delivery room, but rather extend through the first day of life.

Drug Disposition

Late preterm neonates admitted to the intensive care unit often require treatment with potent drugs. Although drug disposition has been inadequately studied in this population, when examined, it appears that late preterm neonates have an immature drug metabolism system when compared with term infants.[70] Thus, they show a significant reduction in drug clearance and prolonged half-lives that require dosage adjustments from those used to treating term newborns. Drug absorption may be reduced in the late preterm infant because of reduced gastric acidity, motility, and bile excretion. Protein binding affects drug actions by influencing drug availability at the target site as only the nonprotein bound form is available to pass membranes for diffusion, bind to receptors, undergo glomerular filtration, and enter the cell for metabolism. Protein binding is reduced in late preterm compared with term infants and can lead to exaggerated drug effects at total drug concentrations usually considered therapeutic.[70] Although late preterm neonates appear mature, several organs responsible for drug disposition are still immature and pharmacokinetic studies in this cohort of neonates have shown significant reductions in drug clearance and prolonged half-lives, exposing them to risks of drug toxicity. Late preterm delivery is often associated with complicated perinatal conditions, such as multiple gestation, maternal diabetes, and chorioamnionitis that can lead to severe neonatal diseases requiring treatment with multiple potent medications. Hence it is important to have more detailed developmental studies of drugs with narrow therapeutic indexes to better guide drug treatment in the late preterm group.

Infection

Compared with term and extremely preterm infants, late preterm neonates are intermediate with regard to immunologic maturity.[71] Although the overall mortality rate from infection is low for late preterm infants, an immature immune system could potentially increase the risk of neonatal complications, prolong hospital stay, and increase health care costs. Late preterm neonates have an increased risk for immaturity of a range of developmental processes resulting in respiratory distress, temperature instability, jaundice, and hypoglycemia. Because many of these clinical findings are some of the common initiating signs of neonatal sepsis, there is an increased likelihood of evaluations for sepsis and antibiotic therapy in late preterm neonates when compared with their term counterparts.[3] Little specific data on the host-defense capability of the near term exist. It is widely known that the host has 2 major systems of defense, the nonspecific innate immune mechanism and the adaptive immune system. Innate immunity includes host defense mechanisms that operate effectively without prior exposure to an antigen. These mechanisms include physical barriers, such as the skin and mucous membrane, which when breached trigger the release of mast cells and tissue macrophages. These mast cells can then activate T lymphocytes, initiating a specific immune response that is often an important component of both innate and acquired immunity. Whether there are subtle changes in mast cell numbers or an optimal mast cell response to an antigen in the near term neonate is unclear. Further research is needed to understand the basic processes of immune development and the complex interactions between the developing human infant and the immune system. This has a potential to provide greater recognition of the many diseases affecting humans, ranging from infections to cancer.[71]

Brain Development

Late preterm neonates have many risks that are common to smaller and more premature infants, such as temperature instability, hypoglycemia, jaundice, feeding inadequacies, and apnea. This is likely because of less mature neural control of respiration and immature brain development when compared with their term counterparts. Nevertheless, there is a paucity of clinical, physiological, neuroanatomic, and neurochemical data in this cohort of neonates.

However, it is known that human brain development is a dynamic process that continues through the end of gestation and beyond. There is a critical period of brain growth and development that occurs in late gestation that is vital to the development of various neural structures and pathways. In fact, approximately 50% of the increase in cortical volume occurs between 34 and 40 weeks of gestation.[72,73] A critical period in the growth and development of the human brain is defined as a period in development where any type of neural insults can lead to profound consequences for later brain development.[74]

The late preterm infant brain at 34 weeks of gestation age weighs only 65% of the term infant's brain and the total brain volume increases linearly with increasing gestation age up to 40 weeks.

Cerebral Cortical Development

The late preterm brain at 34 weeks of gestation weighs only 65% of the term brain, with a 35% increase in growth still needed to reach the term brain weight.[75] Similarly, quantitative magnetic resonance image data have shown that total brain volume increases linearly with increasing gestational age.[75] In early gestation unmyelinated white matter is the predominant neural tissue, which progressively changes to myelinated white matter by late preterm. Gray matter volume increases throughout gestation and specifically has a rapid increase between 36 and 40 weeks of gestation because of neural differentiation and gyral formation.[75] Therefore, in the late preterm infant, the time between 34 and 40 weeks of gestation is critical, because the relative percentage of both gray matter and myelinated white matter to total brain volume increases exponentially. Recognizing that the brain reaches only 65% of term weight by 34 weeks underscores the immaturity of the late preterm brain and its potential vulnerability to multiple insults that interfere with basic mechanisms of neuronal and glial maturation during this time frame.

Cerebellar Development

There are limited data on the relationship between cerebellar development and function on overall neurodevelopmental outcome in preterm infant. The volume of the cerebellum constitutes a larger relative percentage of the total brain volume with increasing gestation age. It is estimated that as much as 25% of the cerebellar volume will develop after the late preterm birth.[76]

Late gestation represents a period of proliferation and migration of the cerebellar granule cells, which constitutes 5 layers of cerebellar cortex and the most prominent of which is the external granular layer, and the inner granular layer appears to be more vulnerable to impairments of blood flow through the period of late preterm development. Injury to these cells will impact subsequent growth and development of cerebellar tissues. Hence these late preterm neonates are vulnerable to cerebellar injury and subsequent associated neurologic sequelae. Further research is needed to determine what extent cerebellar injury contributes to cognitive, motor, and behavioral difficulties in the late preterm population.

Other Considerations of Brain Development and Long-Term Neurodevelopmental Outcomes

Periventricular leukomalacia, a known predictor of adverse neurological outcome, including cerebral palsy and cognitive delays, affects 3% to 4% of preterm infants weighing less than 1500 g. The incidence of periventricular leukomalacia in the late preterm population is not known[77] However, the late preterm neonate is at risk for white matter injury through multiple mechanisms, including developmental vulnerability of the oligodendrocyte, glutamate-induced injury, and injury mediated by cytokines and free radicals.[78] Improved understanding of human brain development has provided us a much clearer understanding of the maturation-dependent vulnerability of the late preterm brain. A significant proportion of development in the cortical gray matter and cerebellum occurs during the last 6 weeks of gestation and it is important for providers to have a clear understanding of the underlying neural pathophysiology to help guide development of neuroprotective strategies for the late preterm infant, which would include close post discharge follow-up at the high-risk clinic and designing appropriate early intervention treatment strategies (eg, occupational therapy, physiotherapy, and speech therapy). The rapidly increasing number of patients born between 34 and 37 weeks gestation highlights the magnitude of the economic impact, if these infants are indeed found to have increased risk for brain injury and adverse neurodevelopmental outcome.

There is a paucity of data on the long-term neurodevelopmental outcome in these groups of neonates and, as the population of the late preterm neonates is steadily growing, clinicians are more carefully evaluating their short- and long-term morbidities. Morse and colleagues[79] recently reported data that late preterm neonates were more likely to have developmental delay within the first 3 years of life and were more likely to be referred for special needs preschool resources. Furthermore, they were more likely to have problems with school readiness. These findings underscore the potential economic and social risks posed by the late preterm infant and the concominant need for additional educational and social services for this growing population. As such, early data indicate that the late preterm infant will need close developmental follow-up despite their apparently healthy presentation. Parents, physicians, child development specialists, and education professionals need to be aware of the risks for possible school underachievement and behavioral problems to provide prompt referrals to early intervention services as needed. Pediatricians can play a crucial role by providing anticipatory guidance for this population.

Rehospitalization

Early postnatal discharge, defined as a hospital stay of less than 48 hours after a vaginal delivery, has been the subject of controversy since the early 1990s. The American Academy of Pediatrics recommends that early postnatal discharge "should be limited to infants who are singleton births between 38 and 42 weeks gestation, who are of birthweight appropriate for gestation age, and who meet other discharge criteria."[80] However, in practice, late preterm infants are usually discharged early. Compared with the term infants, late preterm infants discharged early were at greater risk of neonatal morbidity, with a nearly 2-fold relative risk of being readmitted to a hospital in the neonatal period.[6] Escobar and colleagues[39] found that late preterm neonates with short NICU stays had the highest rehospitalization rates of all infants. In this study the common causes of readmissions were jaundice and feeding issues. Tomashek and colleagues[6] observed that late preterm neonates were 1.5 times more likely to require hospital-related care and 1.8 times more likely than term infants to be readmitted, which increased to 2.2 times if they were breastfed. A recent study involving 7 delivery centers in a managed care organization found that late preterm neonates who were never admitted to the NICU were 3 times more likely than term infants to be readmitted within 2 weeks of discharge.[39] In both of these studies, jaundice and infection were the most common principal diagnoses on hospital readmission and those readmitted with jaundice generally presented earlier than those readmitted with infection. Furthermore, the top 6 emergency room admitting diagnoses for the late preterm cohort seen within the first month of life after discharge were apnea, hyperbilirubinemia, neonatal fever and sepsis workup, respiratory problems, feeding problems, and hypothermia.[81] As a result, there are several initiatives underway to increase general awareness of the risks and problems faced by late preterm neonates within the birth hospital. These initiatives need to extend beyond the nursery to outpatient providers and parents. Emphasis should be placed on feeding management, jaundice, temperature regulation, and assessment for risk of common respiratory problems. Early follow-up with the pediatrician after discharge should be included. Finally, further research must focus on identifying evidence-based recommendations for appropriate discharge timing and post discharge follow-up of late preterm infants.

Costs and Public Health Issues Related to Late Preterm Births

The rate of premature births has steadily increased over the past decade, which is a great clinical and public health concern. An estimate of the total cost of prematurity would include medical costs (initial hospital costs, rehospitalization costs, outpatient care costs associated with a variety of specialists, equipment, home nursing care, etc), nonmedical costs (transportation, housing, special education needs), as well as costs associated with missed opportunity for work and education by parents, patients, and other close family members.[82] One of the major concerns of public health importance is the need to study the long-term neurological and school age outcomes of late preterm infants, because even a minor increase in the rate of neurological disability and scholastic failure in this group can have a huge impact on the health care and educational system. Preterm birth rates, particularly at the earliest gestational ages, are the leading contributor to neonatal morbidity and mortality in the USA, and the national cost estimates for the first several years of life are estimated to exceed $26 billion.[83,84]

One of the major concerns of public health importance is the need to study the long-term neurological and school age outcomes of late preterm infants, which will have a huge impact on the health care and educational system.

Previous analyses have revealed that more recent increases in the USA preterm birth rate were driven by increases in the birth rate of late preterm infants,[1,8] which were associated with a parallel increase in medically indicated preterm birth, induction of labor, and elective Caesarean deliveries.[5,31] These late preterm infants have greater morbidity and total health care costs than term infants, and these differences persist throughout the first year of life.[85] Prevention of "preventable" preterm births should be a high priority public health issue and should be urgently addressed by the health care providers and policymakers.

Conclusions

The obstetrical and the neonatal care of late preterm gestations and its implications for overall health care, educational, and societal costs present many challenges to the health care team and policymakers. The rate of preterm births in the USA increased from 9% in 1981 to 12.8% in 2006,[8] an increase of almost 33%, most of which were caused by increases in the proportion of late preterm infants.[1] Currently, late preterm infants comprise more than 70% of all preterm births and are the fastest growing subgroup of preterm births. The rising rate of late preterm birth has been shown to be associated, in part, with increasing obstetrical intervention. There has been a 50% increase in the rate of Caesarean section over the last decade in USA.[8] Furthermore, it has been observed that the increase in singleton preterm births occurred primarily among those delivered by Caesarean section, with the largest percentage increase in late preterm births. Physicians and patients must be counseled regarding the vulnerability of late preterm infants and the potential for iatrogenic late prematurity morbidity associated with obstetrical interventions. Every effort should be made to make hospital guidelines better to ensure that elective deliveries are not performed before 39 weeks of gestation age. At all gestation ages, the risks of continuing a pregnancy must be carefully balanced against risks of delivery and the associated risk of prematurity. Additionally, it is important to conduct well-designed, adequately powered studies that focus on the underlying reasons for the escalation in preterm births and Caesarean section rates.

Infants who are delivered at late preterm gestations have substantially higher risks for respiratory distress syndrome, transient tachypnea of the newborn, jaundice, and feeding difficulties than do those infants who are born at term.[3,35-37] The processes of adaptation and transition to the extrauterine environment, such as the ability to manage cold stress and maintain euglycemia, rarely are completed in the delivery room and often extend through the first few days of life.[63] This highlights the importance of surveillance for transitional hypoglycemia and hypothermia for late premature infants in the first couple of days of life. Late preterm infants are 1.5 times more likely than term infants to require subsequent hospital-related care and almost twice as likely to be readmitted to hospital in the first 28 days of life.[6]

Late preterm neonates are also more likely to have developmental delay within the first 3 years of life and were more likely to be referred for special needs preschool resources when compared with their term counterparts[79] All of these issues increase total health care costs in the late preterm cohort when compared with the term infants.[85] Thus, even a modest reduction in preterm birth rate, more so in the late preterm gestation age, will reduce the burden of disease and can lead to substantial cost savings.

A comprehensive understanding of all the above discussed issues related to late preterm infants by the physicians, nurses, and hospital administrators is essential to determine the resources to care for a cohort of infants in whom the risk of medical problems are often overlooked.

References

1. Davidoff MJ, Dias T, Damus K, Russel R, Bettegowda VR, Dolan S, et al. Changes in the gestational age distribution among US singleton births: impact on rates of late preterm births, 1992-2002. Semin Perinatol 2006;30:8-15.
2. Mathews TJ, MacDorman MF. Infant mortality statistics from the 2004 period linked birth/infant death dataset. Natl Vital Stat Rep 2007;55(14):1-32.
3. Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near term infants. Pediatrics 2004;114:372-6.
4. Raju TNK, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late preterm (near term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics 2006;118:1207-14.
5. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for Perinatal Care, 5th Edition. Elk Grove Village, IL: American: Academy of Pediatrics; 2005.
6. Tomashek KM, Shapiro-Mendoza CK, Weiss J, kotelchuck M, Barfield W, Evans S, et al. Early discharge among late preterm and term newborns and risk of neonatal morbidity. Semin Perinatol 2006;30:61-8.
7. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, Barfield W, Weiss J, Evans S, et al. Risk factors for neonatal morbidity and mortality among healthy late preterm newborns. Semin Perinatol 2006;30:54-60.
8. National Center for Health Statistics. Final natality data. April 23, 2010 from http://www.marchofdimes.com/peristats.
9. Sabai BM. Preeclampsia as a cause of preterm and late preterm births. Semin Perinatol 2006;30:16-9.
10. Hankins GDV, Longo M. Role of still birth prevention and late preterm births. Semin Perinatol 2006;30:20-3.
11. Hauth JC. Preterm labor and premature rupture of membranes: to deliver or not to deliver. Semin Perinatol 2006;30:98-102.
12. Mathews TJ, Hamilton BE. Mean age of mother, 1970-2000. Natl Vital Stat Rep 2002;51:1-13.
13. Berhman RE. Butler AS, editors. Preterm birth: causes, consequences and prevention. Washington DC: Institute of Medicine of the National Academics; 2006.
14. Russel RB, Petrini JR, Damus K, Mattison DR, Schwarz RH. The changing epidimology of multiple births in the United States. Obstet Gynecol 2003;101(1):129-35.
15. Bailit JL, Love TE, Mercer B. Rising Cesarian rates: are patients sicker? Am J Obstet Gynecol 2004;191(3):800-3.
16. Martin JA, Hamilton BE, Sutton BD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: final data for 2005. CDC Natl Vital Stat Rep 2008;56(6):1-104.
17. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births: final data for 2003. Natl Vital Stat Rep 2005;54(2):1-116.
18. Lee YM, Cleary-Goldman J, D'Alton ME. Multiple gestations and late preterm deliveries. Semin Perinatol 2006;30:103-12.
19. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Munson ML. Births final data for 2002. Natl Vital Stat Rep 2003;52:1-113.
20. Nielson HC, Harvey-Wilkes K, Mackinnon B, Hung S. Neonatal outcome of very premature neonate from multiple and singleton gestations. Am J Obstet Gynecol 1997;177: 653-9.
21. Kaufman GE, Malone PD, Harvey-Wilkes K, Chelmow D, Penzias AS, D'Alton ME. Neonatal morbidity and mortality associated with triplet pregnancy. Obstet Gynecol 1998; 91:342-8.
22. American College of Obstetricians and Gynecologists. Multiple gestation: complicated twin, triplet and high order multifetal pregnancy. ACOG Pract Bulletin No. 56. Obstet Gynecol 2004;104(4):869-83.
23. Newman RB, Krombach RS, Myers MC, McGee DL. Effect of cerclage on obstetric outcome in twin gestations with a shortened cervical length. Am J Obstet Gynecol 2002;186:634-40.
24. Elimian A, Figueroa R, Nigam S, Verma U, Tejani N, Kirshenbaum N. Perinatal outcome of triplet gestation: does prophylactic cerclage make a difference? J Matern Fetal Med 1999;8:119-22.
25. Saunders MC, Dick JS, Brown IM, McPherson K, Chalmers I. The effects of hospital admissions for bed rest on the duration of twin pregnancy: a randomized trial. Lancet 1985;2(8459): 793-5.
26. Norwitz ER, Edusa V, Park JS. Maternal physiology and complications of multiple pregnancy. Semin Perinatol 2005; 29:338-48.
27. Katz M, Robertson PA, Creasy RK. Cardiovascular complications associated with terbutaline treatment for preterm labor. Am J Obstet Gynecol 1981;139(5):605-8.
28. Colton T, Kayne HL, Zhang Y, Heeren T. A metaanalysis of home uterine activity monitoring. Am J Obstet Gynecol 1995; 173(5):1499-505.
29. Miesnik SR, Reale BJ. A review of issues surrounding medically elective Cesarian section delivery. J Obstet Gynecol Neonatal Nurs 2007;36(6):605-15.
30. American College of Obstetricians and Gynecologists. Management of preterm labor. Practice Bulletin. Int J Gynaecol Obstet 2003;82(1):127-35.
31. NIH state of the science conference. Cesarean delivery on maternal request Available at: http://consensus.nih.gov.
32. Filley RA, Hadlock FP. Sonographic determination of gesta-

tional age. In: Callen PW, editor. Ultrasonography in obstetric and gynecology, 4th Edition. Philadelphia: WB Saunders; 2000.
33. Laing FC, Frates MC. Ultrasound evaluation in the first trimester of pregnancy. In: Callen PW, editor. Ultrasonography in obstetric and gynecology, 4th Edition. Philadelphia: WB Saunders; 2000.
34. Hamilton BE, Martin JA, Sutton RD. National Vital statistics Reports. Births: Preliminary data for 2003. 2003;53(9):1-6.
35. Sarici SU, Serdar MA, Korkmaz A, Erdem G, Oran O, Tekinalp G, et al. Incidence, course and prediction of hyperbilirubinemia in near term and term infants. Pediatrics 2004; 113(4):775-80.
36. Seubert DE, Stetzer BP, Wolfe HM, Treadwell MC. Delivery of the marginally preterm infant: what are the minor morbidities? Am J Obstet Gynecol 1999;181:1087-91.
37. Mclntire D, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol 2008;111(1):34-41.
38. Angus DC, Linde-Zwirble WT, Clermont G, Griffin MF, Clark RH. Epidemiology of neonatal respiratory failure in the United States: projections from California and New York. Am J Respir Crit Care Med 2001;164:1154-60.
39. Escobar GJ, Greene JD, Hulac P, Kincannon E, Bischoff K, Gardner MN, et al. Rehospitalization after birth hospitalization: patterns among infants of all gestations. Arch Dis Child 2005;90:125-31.
40. Clark RH. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. J Perinatol 2005;25:251-7.
41. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. Semin Perinatol 2006;30:34-43.
42. Goldenberg RL, Nelson K. Iatrogenic respiratory distress syndrome. An analysis of obstetric events preceding delivery of infants who develop respiratory distress syndrome. Am J Gynecol 1975;123:617-20.
43. Hack M, Fanaroff AA, Klaus MH, Mendelawitz BD, Merkatz IR. Neonatal respiratory distress following elective delivery. A preventable disease? Am J Obstet Gynecol 1976;126:43-7.
44. Maisels MJ, Rees R, Marks K, et al. Elective delivery of term fetus: an obstetrical hazard. L Am Med Assoc 1997;238:2036-9.
45. Heritage CK, Cunningham MD. Association of elective Cesarian delivery and persistent pulmonary hypertension of the newborn. Am J Obstet Gynecol 1985;152:627-9.
46. Keszler M, Carbone MT, Cox C, Schumacher RE. Severe respiratory failure after elective Cesarian delivery: a potentially preventable condition leading to ECMO. Pediatrics 1992;89:670-2.
47. Bailey S, Hendricks-Munoz K, Mally P. Incidence of respiratory distress syndrome (RDS) among term and late preterm (LPT) neonates. EPAS 2009;502.
48. De Luca R, Boulvain M, Irion O, Berner M, Pfister RE. Incidence of early neonatal mortality after late pre-term and term Cesarian delivery. Pediatrics 2009;123(6):e1064-71.
49. Kitsommart R, Janes M, Mahajan V, Rahman A, Seideitz W, Wilson J, et al. Outcomes of late-preterm infants: a retrospective, single-centered, Canadian study. Clin Pediatr 2009; 48(8):844-50.
50. de Almeida MFB, Guinsburg R, Costa JO, Anchieta LM, Freire LM, Junior DC. Resuscitative procedures at birth in late preterm infants. J Perinatol 2007;27:761-5.
51. Neu J. Gastrointestinal maturation and feeding. Semin Perinatol 2006;30:77-80.
52. Kien CL, McClead RE, Cordero L Jr. Effects of lactose intake on lactose digestion and colonic fermentation in preterm infants. J Pediatr 1998;133:401-5.
53. Kien CL. Digestion, absorption and fermentation of carbohydrates in the newborn. Clin Perinatol 1996;23:211-28.
54. Shivpuri CR, Martin RJ, Carlo WA, Fanaroff AA. Decreased ventilation in preterm infants during oral feeding. J Pediatr 1983;103:285-9.
55. Berseth CL. Gastrointestinal motility in the neonate. Clin Perinatol 1996;23:179-90.
56. Escobar GJ, Gonzales VM, Armstrong MA, Folck BF, Xiong B, Newman TB. Rehospitalization for neonatal dehydration: a nested case control study. Arch Pediatr Adolesc Med 2002;156:155-61.
57. Adamkin D. Feeding problems in the late preterm infant. Clin Perinatol 2006;33:831-7.
58. Kaplan M, Muraca M, Vreman HJ, Hammerman C, Vilei MT, Rubaltelli FF, et al. Neonatal bilirubin production-conjugation imbalance: effect of glucose 6 dehydrogenase deficiency and borderline prematurity. Arch Dis Child Fetal Neonatal Ed 2005;90:F123-7.
59. Kawade N, Onish S. The prenatal and post natal development of UDP glucuronyltransferase activity towards bilirubin and the effect of premature birth on this activity in the human liver. Biochem J 1981;196:257-60.
60. Gartner LM, Herschel M. Jaundice and breastfeeding. Pediatr Clin North Am 2001;48:389-99.
61. Gartner LM, Snyder RN, Chabon RS, Bernstein J. Kernicterus: high incidence in premature infants with low serum bilirubin concentrations. Pediatrics 1970;45:906-17.
62. Bhutani VK, Johnson LH, Maisels MJ, Newman TB, Phibbs C, Stark AR, et al. Kernicterus: epidemiological strategies for its prevention through systems-based approaches. J Perinatol 2004;24:650-62.
63. Laptook A, Jackson G. Cold stress and hypoglycemia in late preterm infant: impact on nursery admission. Semin Perinatol 2006;30:24-7.
64. Adamson SK Jr, Gandy GM, James LS. The influence of thermal factors upon oxygen consumption of the newborn human infant. J Pediatr 1965;66:495-508.
65. Dahm LS, James LS. Newborn temperature and calculated heat loss in the delivery room. Pediatrics 1972;49:504-13.
66. Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. Arch Dis Child 1992;67:357-65.
67. Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birthweight and gestational age. Pediatrics 1971;47:831-8.
68. Amiel-Tison C, Allen MC, Lebrun F, Rogowski J. Macropremies: underpriviliged newborns. Ment Retard Disabil Res Rev 2002;8:281-92.
69. Cornblath M, Ichord R. Hypoglycemia in the neonate. Semin Perinatol 2000;24(2):136-49.
70. Robert MW. Drug disposition in the late pre term (near term) newborn. Semin Perinatol 2006;30:48-51.

71. Clapp DW. Developmental regulation of the immune system. Semin Perinatol 2006;30:69-72.
72. Guihard-Costa AM, Larroche JC. Differential growth between the fetal brain and its infratentorial part. Early Hum Dev 1990;23:27-40.
73. Kinney HC. The near term (late preterm) human brain and risk for periventricular leucomalacia: a review. Semin Perinatol 2006;30:81-8.
74. Hannah C. Kinney, the near term (late preterm) human brain and risk for periventricular leukomalacia: a review. Semin Perinatol 2006;30:81-8.
75. Huppi PS, Warfield S, Kikinis R, Barnes PD, Zientara GP, Jolesz FA, et al. Quantitative MRI of brain development in premature and mature brain. Ann Neurol 1998;43:224-35.
76. Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, et al. Late gestation cerebellar growth is rapid and imoeded by premature birth. Pediatrics 2005;115:685-95.
77. Rezaie P, Dean A. Periventricular leucomalacia, inflammation and white matter lesions within the developing nervous system. Neuropathology 2002;22:106-32.
78. Folkerth RD, Haynes RL, Borenstein NS, Belliveau RA, Trachtenberg F, Rosenberg PA, et al. Developmental lag in superoxide dismutases relative to other antioxidant enzymes in premyelinated human white matter. J Neuropathol Exp Neurol 2004;63:990-9.
79. Morse SB, Tang Y, Roth J. School age outcomes and healthy late preterm neonate. Pediatr Res Suppl 2006;158;Abstract 4355.
80. American Academy of Pediatrics, Committee on fetus and newborn. Hospital stay for healthy term newborns. Pediatrics 2004;113:1434-6.
81. Jain S, Cheng J. Emergency Department visits and rehospitalizations in late preterm infants. Clin Perinatol 2006;33:935-45.
82. Petrou S, Sach T, Davidson L. Long term costs of preterm births and low birthweight: results of a systematic review. Child Care Helath Dev 2001;27:97-115.
83. Slattery MM, Morrison JJ. Preterm delivery. Lancet 2002; 360:1489-97.
84. Callaghan WM, MacDorman MF, Rasmussen SA. The contribution of preterm birth to infant mortality rates in the United States. Pediatrics 2006;118(4):1566-73.
85. McLaurin KK, Hall CB, Jackson EA, Owens OV, Mahadevia PJ. Persistence of morbidity and cost differences between late preterm and term infants during the first year of life. Pediatrics 2009;123:653-9.