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Late Preterm Infants: Near Term But Still in a Critical Developmental Time Period

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KEY WORDS

late preterm infants, neurodevelopmental, respiratory, outcomes

ABBREVIATIONS

BPD—bronchopulmonary dysplasia
FRC—functional residual capacity
GA—gestational age
IUGR—intrauterine growth retardation
LP—late preterm
PVL—periventricular leukomalacia
RDS—respiratory distress syndrome
RSV—respiratory syncitial virus
SGA—small for gestational age
TTN—transient tachypnea of the newborn

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abstract

Late preterm (LP) infants are defined as those born at 34-0/7 to 36-6/7 weeks' gestational age. LP infants were previously referred to as near term infants. The change in terminology resulted from the understanding that these infants are not fully mature and that the last 6 weeks of gestation represent a critical period of growth and development of the fetal brain and lungs, and of other systems. There is accumulating evidence of higher risks for health complications in these infants, including serious morbidity and a threefold higher infant mortality rate compared with term infants. This information is of critical importance because of its scientific merits and practical implications. However, it warrants a critical and balanced review, given the apparent overall uncomplicated outcome for the majority of LP infants.

Others reviewed the characteristics of LP infants that predispose them to a higher risk of morbidity at the neonatal period. This review focuses on the long-term neurodevelopmental and respiratory outcomes, with the main aim to suggest putative prenatal, neonatal, developmental, and environmental causes for these increased morbidities. It demonstrates parallelism in the trajectories of pulmonary and neurologic development and evolution as a model for fetal and neonatal maturation. These may suggest the critical developmental time period as the common pathway that leads to the outcomes. Disruption in this pathway with potential long-term consequences in both systems may occur if the intrauterine milieu is disturbed. Finally, the review addresses the practical implications on perinatal and neonatal care during infancy and childhood. *Pediatrics* 2013;132:741–751

INTRODUCTION

Late preterm (LP) infants are defined as those born at 34-0/7 to 36-6/7 weeks gestational age (GA).[1] LP infants are born near term, but are immature.[2,3] The late premature birth interrupts normal in utero fetal development during the last 6 weeks of gestation that represents a critical period of growth and development of the fetal brain and lungs. Kinney defined a critical period as a time-sensitive, irreversible decision point in the development of a neural structure or system in which deprivation of the normal environment interrupts the maturational trajectory of the structure/system.[4] We find this definition attractive and applicable also to the respiratory system and likely to other systems as well. This review will focus on the neurodevelopmental and the respiratory systems as models for fetal and neonatal maturation.

LATE PREMATURITY: SCOPE OF THE PHENOMENON, MORTALITY, AND NEONATAL MORBIDITY

LP newborns comprise the fastest growing subset of neonates, accounting for ~74% of all preterm births and ~8% to 9% of total births in the United States.[5] There is accumulating evidence for higher risks for early and late health complications in LP infants, including a threefold higher infant mortality rate compared with term infants (7.7 vs 2.5 per 1000 live births).[2,3,5–10]

A US multistate study showed that infants born at 32 to 36 weeks' gestation had more than a twofold risk for having congenital malformations than their term counterparts.[11] It was reported that during infancy LP infants were ~4 times more likely than term infants to die of congenital malformations (leading cause).[8] Congenital malformation can lead to either spontaneous or physician-induced preterm delivery. Preterm delivery can increase the risk for death among infants who have anomalies. However, when Kramer et al excluded infants with congenital anomalies from their cohort, the relative risk for death in LP infants decreased only slightly and was still significantly higher compared with term infants.[6]

Intrauterine growth retardation (IUGR) is often the cause for LP birth and is thus more common among LP infants compared with term infants,[12–14] and in itself constitutes a prenatal cause for increased risk for death, which was not considered by all the population-based studies. It was shown that being small for gestational age (SGA) substantially increases the already higher mortality of LP and early term newborns and that this increased risk cannot be fully explained by an increased prevalence of lethal congenital conditions among SGA LP newborns.[15] Nevertheless, even when excluding congenital malformations and being SGA, the relative risk for death is higher among LP infants.[15]

Maternal prenatal and immediate postnatal complications are associated with increased neonatal morbidities. Chorioamnionitis, premature rupture of membranes, maternal morbidities (hypertension, preeclampsia, diabetes), and maternal smoking are more common in LP infants.[16–19] Newborn bacterial sepsis, complications of placenta, cord, and membranes,[8] antepartum hemorrhage, and hypertensive disorders were also associated with the increased mortality of LP infants.[20] In addition, compared with infants delivered via planned vaginal delivery, LP infants delivered via elective cesarean delivery had significantly higher rates of mortality, risk for special care admission, and respiratory morbidity.[21] The precise mechanisms that render LP infants more vulnerable to death likely vary with circumstances and are hard to deduce from existing epidemiologic studies.

Despite the low absolute risk for death and other complications in LP infants, factoring in their large numbers compared with more extreme preterm infants, the relative risk translates into significant medical, emotional, and economic impact at the population level.[12,22]

Most LP infants (~80%) will have a neonatal course with no significant complications.[23] However, compared with term neonates, LP newborns are at increased risk for the following: resuscitation at birth,[16] feeding difficulty, jaundice, hypoglycemia, temperature instability, apnea, and respiratory distress.[2,3,6,12,16,24,25] These morbidities variably result in workup for sepsis evaluations and antibiotic therapy, intravenous fluid administration, ventilatory support, and increased length of stay (~30%).[2,12,25] Predisposing factors to these morbidities were reviewed by Engle et al.[2] LP infants were also found to have increased rehospitalization rate[2,6,7,24,26] and more use of medical resources during their first year of life, such as respiratory syncitial virus (RSV) prophylaxis.[27]

The rate of complications decreases with progression of gestational age through the LP period.[6] Shapiro-Mendoza et al compellingly demonstrated the relationship between advancing age and morbidity, reporting a sevenfold increase (22.2% vs 3.0%) in neonatal morbidities in LP infants compared with term infants.[23] Respiratory complications are the prime morbidities of LP infants.[10,12,16,24,25] A large retrospective study found that the odds of respiratory distress syndrome decreased significantly with each advancing week of gestation up to 38 weeks compared with 39 to 40 weeks.[28] Despite a relatively low absolute risk for RDS (10.5%) or transient tachypnea of the newborn (TTN) (6.4%) at 34 weeks compared with more premature infants, this rate poses an increased risk for LP infants when

compared with term infants (0.3% for RDS and TTN).[29]

LONG-TERM MORBIDITY OF LP INFANTS

Neurodevelopmental Long-Term Outcome

Neurodevelopmental Outcome: Clinical Evidence

LP infants are often perceived to have similar risks for developmental problems as neonates born at term. Because the rate of intraventricular hemorrhage is low (0.2% to 1.4%),[10,29,30] albeit higher than in term infants[10] and their rate of periventricular leukomalacia (PVL) is low although practically unknown,[4,31] they do not undergo routine brain ultrasonography. Furthermore, the common practice is not to follow them in neurodevelopmental centers.

Recently, however, there is growing concern that these infants are more vulnerable to brain injury than previously appreciated. PVL is not restricted to the very prematurely born infant, and occurs in the LP (and term) infants as well.[32–35] Some studies reported a threefold increased risk for developing cerebral palsy in LP infants compared with term infants.[10,36]

There is mounting evidence that LP infants have more subtle neurodevelopmental issues such as inferior academic performance or behavioral problems.[37–45] McGowan et al reviewed the literature relating to early childhood development of LP infants born at 34 to 36 weeks' gestation at 1 to 7 years of age.[45] Of 4581 studies, 10 (3 prospective and 7 retrospective cohorts) were included. They concluded that LP infants compared with term infants were at increased risk for adverse developmental outcomes and academic difficulties up to 7 years of age, but that a systematic measurement of early childhood outcomes was lacking. We tabulated the results of the recent literature (Table 1) supporting higher risk for decreased developmental and school performance and academic abilities of LP infants.[37–44] Notably, the results of other studies were less conclusive.[46,47]

The available data are weighted toward a concern regarding the long-term neurodevelopmental outcome of LP infants. Given, however, that the data rely mostly on retrospective studies, and that not all studies focused on healthy LP infants, a need for prospective large studies is obvious.

Mechanisms of Neurologic Effects of LP Birth

A number of possibilities could be postulated as playing a role in the causation of long-term neurodevelopmental abnormalities in LP infants and include: (1) prematurity itself leading to maturation outside the uterine milieu, (2) the morbidity associated with LP, and (3) the primary cause of premature labor.

The last half of gestation (including the late prematurity period) was described as a "critical period" for brain development and characterized by rapid and/or dramatic changes in 1 or more molecular, neurochemical, and/or structural parameters (Fig 1).[4,48,49] The notion of "hierarchy of vulnerability" provides the proper perspective, and denotes that although LP infants are more mature than very preterm infants, their brain is still immature, and can be damaged under some adverse conditions.[4] Brain development is not a linear process, and the critical developmental changes that occur in the brain in the last weeks of gestation can easily be underappreciated. To what extent the extrauterine milieu affects the process is not well studied. Brain weight at 34 weeks is only 65% of that of the term brain and gyral and sulcal formation is incomplete. Cortical volume increases by 50% between 34 and 40 weeks' gestation, and 25% of cerebellar development occurs during this time period (Fig 1).[4,48–50] Therefore, in the LP infant, the period between 34 and 40 weeks' gestation is critical, because the relative percentage of both gray

TABLE 1 Long-Term Neurodevelopmental Outcome

Reference	Study Design	Participants	Main Outcomes
Chyi et al[37]	Retrospective	767 LP/13 671 term	Increased risk for below-average reading competence at all grade levels, increased need for individualized education programs at early school ages, and increased need of special education
Gray et al[38]	Prospective	260 LP /General population	Increased rate of behavior problems at age 8 yr
Huddy et al[39]	Retrospective	83 LP	Increased rate of hyperactivity, behavioral, or emotional problems
Woythaler et al[40]	Prospective	1200 LP/6300 term	Increased risk for mental or physical developmental delay at age 24 mo
Morse et al[41]	Retrospective	7152 LP/152 661 term	Increased risk for developmental delay or school-related problems through age 5 yr
Lipkind et al[42]	Retrospective	13 207 LP/199 599 term	Increased need for special education and lower adjusted math and English scores at school age. Linear association between GA and test scores through 39 wk gestation
Quigley et al[43]	Retrospective	537 LP/6159 term	Increased risk for poorer educational achievement at age 5 yr
Talge et al[44]	Retrospective	168 LP/168 term	Increased risk for behavioral problems and lower IQ at age 6 yr
Odd et al[46]	Prospective	741 (32–36 wk)/13 102 term	Despite an increased risk for special educational needs, there was little evidence of a reduction in IQ, memory, or attention measures at school age
Gurka et al[47]	Prospective	53 LP/1245 term	No difference regarding cognition, achievement, behavior, and socioemotional development throughout childhood

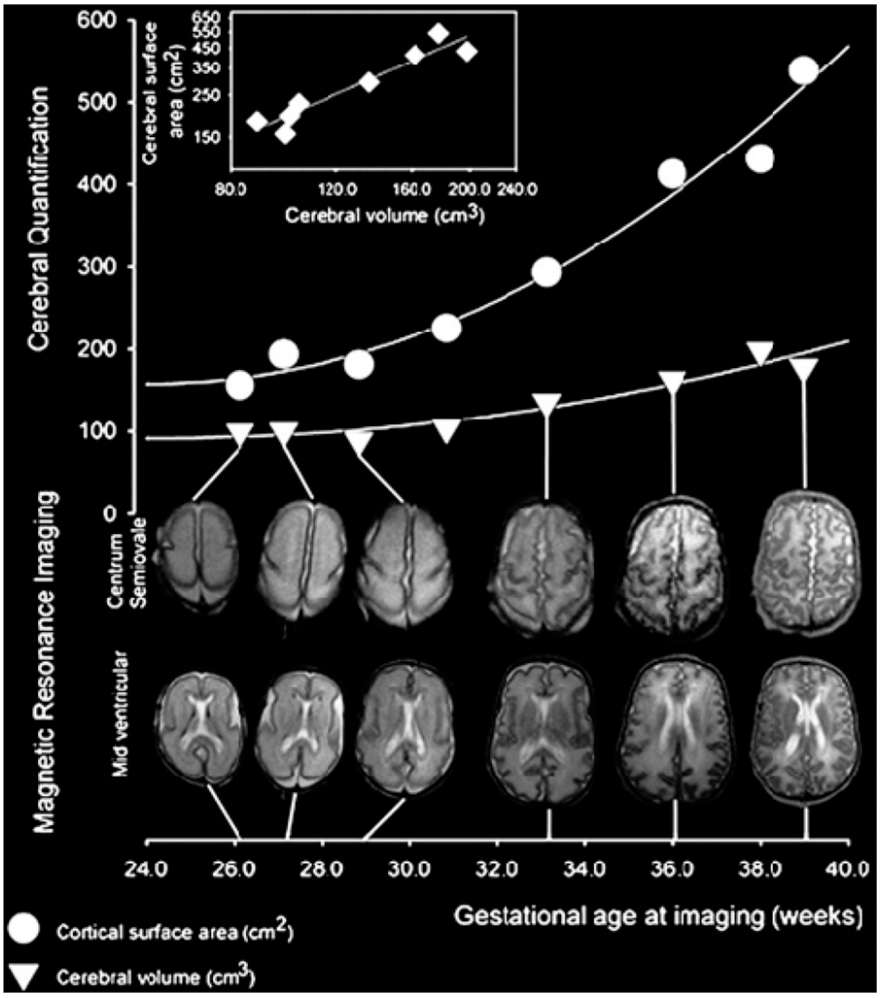

FIGURE 1
Changes in brain volume and maturation with increasing gestational age. (From Kapellou et al.[49]).

matter and myelinated white matter to total brain volume increases exponentially.[31,50] The LP infant is at risk for white matter injury through multiple potential mechanisms, including developmental vulnerability of the oligodendrocyte, glutamate-induced injury, cytokine- and free radical-mediated injury, and the absence of maturation-dependent antioxidant enzymes that regulate oxidative stress.[31] Synaptogenesis and dendritic arborization are occurring, and are likewise incomplete in the LP brain compared with the term brain, albeit not to the degree seen in the very premature brain.[51]

Beyond the question of whether the extrauterine environment would be an inherently inhospitable milieu to normal development, multiple compounding factors in the extrauterine environment could be related to the developmental immaturity of LP infants and amplify the risk for brain injury and subsequent neurologic sequelae. These include the risk for development of intraventricular hemorrhage and PVL, hypoxic respiratory failure, hypoglycemia, hyperbilirubinemia, infection, and chorioamnionitis. The LP neonate has a two- to fivefold increased risk for developing significant hyperbilirubinemia.[31,52] When compared with term newborns with similar bilirubin levels, LP infants are more likely to have severe neurologic sequelae and neurotoxicity at earlier postnatal ages. This most likely is secondary to a combination of factors, including immaturity of conjugation and enzymatic pathways, immature feeding patterns, and the age-dependent susceptibility of developing neurons and astrocytes to bilirubin-induced injury. On the reassuring side, a recent prospective study reported that there were no significant differences in early childhood development (at 3 years of age) between LP infants who received neonatal intensive or high-dependency care and those who did not.[53] This study did not have a control group of term infants, but as is, it may be pointing toward factors other than short-term morbidities as playing a role in the long-term outcomes.

The primary cause of premature labor might also impair neurodevelopmental outcome. LP infants compared with term infants have higher rates of congenital malformations,[8,11] IUGR,[12–14] high-risk pregnancies (preeclampsia, hypertension, diabetes), chorioamnionitis, and maternal smoking.[16–19] Each of these factors, although not specific to LP infants, could potentially be associated with poor neurodevelopmental outcome or behavioral problems. For example, SGA was associated with poor outcome in extremely low birth weight infants[54] and in term infants,[55] but the few studies that assessed the correlation between SGA and poor long-term neurodevelopmental outcome were negative for LP infants.[55,56] Although intuitively correct, larger, prospective studies focusing on LP infants are needed to assess whether findings from very preterm or term infants are generalizable to this subgroup of infants.

To summarize, LP infants are at risk for long-term neurodevelopmental morbidities. The primary causes of late prematurity and prenatal factors as well as congenital malformations and IUGR may expose the LP infant to short- and

long-term sequelae (Fig 2A). The late prematurity itself puts the LP infant at risk for neonatal morbidities, which are usually of modest severity compared with more extreme premature infants, but may contribute to the insult. The interruption of the in utero maturational process of the brain, which is in a critical period, is probably the main reason for the long-term neurodevelopmental outcomes.

Respiratory Long-Term Outcome

Respiratory Outcome: Clinical Evidence

A number of publications attempted to address the question whether late prematurity affects the respiratory system in the long term (Table 2).[57–64] Several studies reported an association of preterm birth (30–36 weeks' GA) without clinical lung disease with altered lung development and function.[59,60,62–64] Friedrich et al[64] in a longitudinal study found that despite normal lung volume, healthy preterm infants had persistently reduced airflow through the age of 16 months and concluded that preterm birth in itself was associated with altered lung development. A single study showed a potential improvement, especially for large airway function, with advancing age.[61]

Whether LP birth is associated with airway disease such as asthma in early childhood remains controversial. Abe et al[65] did not find an association between LP and physician-diagnosed asthma. Similarly, a Swedish national cohort study failed to find an association between LP birth at 33 to 36 weeks' gestation and asthma medications in young adults.[66] Conversely, Goyal et al[67] in a retrospective cohort study using electronic health record data from a primary care network, demonstrated that birth at late-prematurity might be a risk factor for the development of asthma within the first 18 months of life. Escobar et al[68] in a retrospective cohort study reported that LP birth was associated with an increased risk for recurrent wheeze in the third year of life. The different findings could result from the different methods of asthma diagnosis, age groups at diagnosis, and from the difficulties in diagnosing asthma in early childhood. A recent large prospective cohort study showed that the number of hospitalizations caused by respiratory problems during the first year of life was doubled in moderately preterm (32–36 weeks' GA) compared with term infants.[69] At preschool age, moderately preterm infants revealed more nocturnal cough or wheeze during or without a cold and increased use of inhaled steroids. At the age of 5 years, rates of respiratory symptoms between moderate and early preterm-born (<32 weeks' GA) children were similar; both were higher than in term-born children. The most important risk factors for continuing respiratory problems in moderately preterm-born children were eczema, respiratory problems and passive smoking during the first year of life, higher social class, and a positive family history of asthma.

Some of the studies reporting on the long-term outcomes of the respiratory system included infants of less than 34 weeks' GA. Recognizing that the risks are decreasing with advancing age,

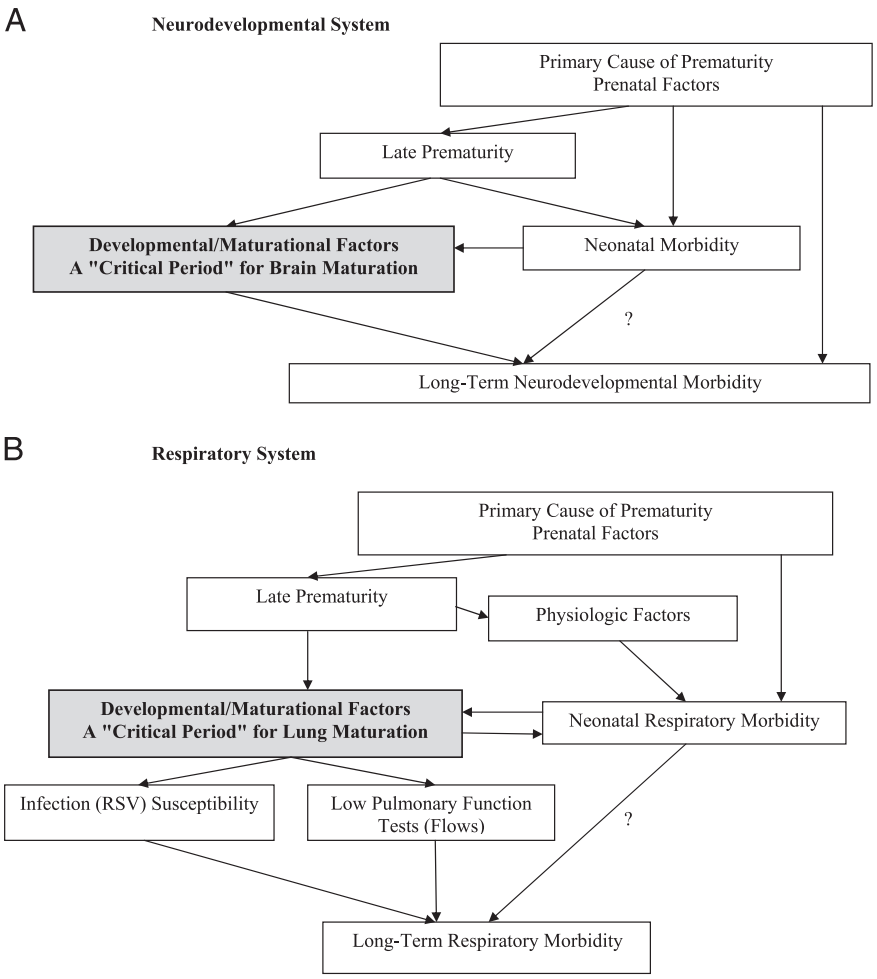

FIGURE 2
Parallelism in the trajectories of lung and neurodevelopment and evolution that may suggest the "critical developmental time period" as the common pathway that leads to the outcomes. A, The neurodevelopmental system. B, The respiratory system.

TABLE 2 Long-Term Respiratory Outcome

Reference	Study Design	Participants	Main Outcomes
McEvoy et al[59]	Prospective	31 LP (33–36 wk)/31 term	Healthy LP infants studied at term-corrected age have decreased compliance and increased resistance
Todisco et al[60]	Case control, matched siblings	34 LP (34–36 wk)/34 term	Pulmonary functions at age ~11 yr revealed air trapping but no significant difference in bronchial responsiveness in healthy LP. Maternal smoking during pregnancy was more prevalent in the preterm children with impaired respiratory functions
Kotecha et al[61]	Prospective	81/49 infants: 33–34 wk, 248/132 infants: 35–36 wk, 6308/4284 infants: term, at 8–9 yr and 14–17 yr, respectively	At 8–9 yr of age, measures of forced expiratory spirometry are lower in children born at 33–34 wk GA compared with children born at term and are of similar magnitude to those in the extremely preterm infants. Infants born at 35–36 wk GA had the same PFTs as term infants. By 14–17 yr, measures of airway function in children born at 33–34 wk GA were similar to those in children born at term with the exception of forced expiratory flow rate between 25% and 75% of exhaled vital capacity
Hoo et al[62]	Prospective	24 infants 33.2±2.2 wk	Preterm delivery is associated with altered airway development during early infancy (reduced maximal expiratory flow at functional residual capacity up to 12 mo) in healthy preterm infants
Mansell et al[63]	Case control	18 premature infants with RDS/26 premature infants without RDS/18 term	Although no difference in PFT between infants with and without RDS, FEV1 and specific airway conductance were significantly reduced in the premature infants compared with children born at term when studied by spirometry at age 6–9 yr
Friedrich et al[64]	Prospective	26 infants (30–34 wk)/24 infants at term	Healthy infants born prematurely demonstrate decreased forced expiratory flows and normal forced vital capacities in the first and second years of life

FEV1, forced expiratory volume at 1 s; PFT, pulmonary function tests.

caution needs to be exercised when generalizing their findings to the entire group of LP infants.

Mechanisms of Respiratory Effects of LP Birth

Three factors play a role in the respiratory vulnerability of LP infants[57]: (1) prematurity with its inherent developmental and consequently physiologic components, (2) heightened rate of respiratory morbidity in the neonatal period and prenatal factors, and (3) increased susceptibility to RSV.[70–73]

Lung development occurs mostly in utero. LP infants are born within the final stages of the saccular stage (26–36 weeks of gestation).[74] Premature birth during this critical respiratory maturation period may result in significant alteration in lung function and physiology. Normal in utero lung development occurs according to a highly programmed sequence in a stable milieu, notably and importantly, one that is profoundly more hypoxic relative to the atmosphere. This hypoxic environment represents the norm for lung organogenesis, including vascular development.[74–77] Early events of trophoblast differentiation are oxygen regulated.[78] It is safe to assume that there is an array of other yet to be determined hormonal and biochemical factors that play a role in regulating the sensitive choreography of lung development and differentiation in utero and are altered or absent after delivery.

To understand the mechanisms that possibly explain the morbidity in LP infants, it is necessary to understand lung physiology at this stage of their development.[57] In early life, the lung-chest wall equilibrium results in a mechanically determined functional residual capacity (FRC) that is low relative to older children and adults and is an important determinant of age-related vulnerability to hypoxia. Gradual stiffening of the chest wall and with it the transition from an actively maintained FRC to one that is mechanically determined occurs in term infants late in the first year and into the second year of life.[79–81] An additional crucial mechanism that secures airway patency and thus adequate maintenance of FRC is airway tethering.[57,81,82] Tethering is the element that couples lung volume to airway patency, and thus as lung volumes increase, airway diameter, and hence expiratory flows, are increased. Total lung volume undergoes rapid changes during the last trimester of gestation (at 34 weeks it only reaches 47% of the final volume at maturity), the air-space walls decrease in thickness, and a fourfold increase in air-space surface area occurs (1–4 m^2).[74] These volume changes have direct mechanical implications in reducing the vulnerability caused by a low and unstable FRC. Maturation of the alveolar network improves parenchymal elastance and therefore airway-tethering. These immaturities add up to be elements in the vulnerability of late preterm infants to respiratory morbidity in the short term and could contribute to the long-term outcomes if the

predestined evolution of the maturational process is aborted or altered in the extrauterine milieu.

The morbidities during the neonatal period could also be affected by prenatal factors. Epidemiologic studies demonstrate that IUGR and low birth weight are associated with impaired lung function and increased respiratory morbidity from infancy throughout childhood and into adulthood.[83] Operative delivery, maternal diabetes, and chorioamnionitis also increased RDS risk in LP infants.[84,85] Gestational hypertension or preeclampsia appear to protect from neonatal respiratory morbidity, but higher rates of cesarean section diminish this protective effect,[19] and others reported an opposite effect.[20,23] Chorioamnionitis, which is more common in LP infants,[16–19] may have a complex effect on the pulmonary system. A low-grade inflammatory stimulus in utero may prime the fetal lung for accelerated maturation. Depending on the severity of inflammatory injury to the alveolar-capillary unit, however, serum proteins leak into the airways and induce surfactant inactivation. After this intrauterine first hit, the immature infant may develop a more severe RDS.[86] Chorioamnionitis and cytokine exposure in utero, added to neonatal lung injury because of respiratory morbidity can lead to a pulmonary inflammatory response in the immature lungs of very preterm infants, contributing to the development of "new BPD".[87] It has yet to be determined to what extent these processes described in very preterm infants affect LP infants. TTN is more common in LP infants,[27] is associated with elective cesarean delivery,[88,89] and is associated with childhood wheezing[90] and asthma.[91,92] While possible, it is not known if all these prenatal and neonatal factors also affect the long-term respiratory outcome of LP infants. The possible mechanism is also obscure; namely, it is unclear whether this is a result of a direct injury or a multi-hit phenomenon on the developing respiratory system.

The third factor contributing to the respiratory vulnerability of LP infants is increased susceptibility to RSV infection as a consequence of altered lung development.[70–72] This is thought to be primarily related to the failure to develop an adaptive cytotoxic T-lymphocyte response and inefficient innate immune responses that clear the virus from the airways.[73] Non-randomized trials in preterm infants (~30 ± 2 weeks' GA) suggested that the prevention of lower respiratory tract illness caused by RSV reduced subsequent recurrent wheeze in infants without a family history of atopy, but showed no effect in infants with a family history of atopy.[93,94] In a recent study in otherwise healthy 33 to 35 weeks' GA preterm infants, palivizumab treatment resulted in a significant reduction in wheezing days during the first year of life, even after the end of treatment. These findings implicate RSV infection as an important mechanism of recurrent wheeze during the first year of life in such infants.[95]

Long-term persistence of early decrease in PFT was demonstrated by a longitudinal follow-up into early adulthood for an unselected random population in the Tucson Children's Respiratory Study.[96] These observations suggest that the notion of a "critical developmental period" for the respiratory system does exist. Deficits in lung function during early life, especially if associated with lower respiratory illnesses (especially RSV), increase the risk for chronic obstructive pulmonary disease later in adult life.[97]

To summarize (Fig 2B), prematurity with its physiologic deficiencies may affect and contribute to the susceptibility to neonatal respiratory morbidity of LP infants. Prenatal factors could also affect the morbidity in the neonatal period, and to a certain degree the long-term respiratory outcome. Although the development-dependent physiologic factors largely resolve over time and the overall morbidity is usually not very significant, it is unclear how these contribute to future outcome. However, interrupting the critical developmental period by LP delivery is probably the main reason for the prematurity-related persistent abnormalities in the respiratory system. LP infants are more vulnerable to viral respiratory infections, particularly RSV, which are more severe in these infants versus term infants. The pernicious combination of RSV bronchiolitis affecting an a priori compromised lung/airway of LP infants may have a lasting effect on respiratory function and consequent long-term clinical morbidity.

PRACTICAL IMPLICATIONS

The American College of Obstetricians and Gynecologists has recommended that elective delivery should only take place after 39 weeks in well-dated pregnancies.[98] When feasible, prevention of late prematurity within safety guidelines for the mother and the fetus should be the goal. The implementation of hospital quality improvement programs has successfully reduced the occurrence of elective early-term and late-preterm deliveries, as well as associated neonatal morbidity and mortality.[99]

New approaches to decrease the respiratory morbidity in LP infants are needed. Antenatal corticosteroids were shown to significantly reduce admissions to special care units in term infants delivered by elective cesarean section.[100] In LP infants, antenatal steroids did not lower the rate of either RDS or TTN and did not affect the need for, type, and means of ventilatory support.[101] An NIH study (ClinicalTrials.gov Identifier: NCT01222247) comparing a single course

of antenatal steroids versus placebo is ongoing.

Once a decision is made to deliver LP infants they should be monitored for the possible complications at an appropriate set-up. No study has determined if this should be done in the nursery, in the intermediate care, or in the NICU according to specific GA groups.

From 1995 to 2000, early discharge (less than 48 hours after vaginal delivery) of LP infants had decreased from 71% to 40% in United States.[102] The AAP published detailed guidelines for the care of LP infants.[2] These guidelines suggest that these infants should not be discharged before 48 hours of birth.[2] Early discharge places these infants at greater risk for complications such as rehospitalization, particularly in breastfed or first-born infants.[2,3,103] The AAP recommends a follow-up visit 24 to 48 hours after hospital discharge for LP infants, given their increased risk for rehospitalization secondary to jaundice, feeding difficulties, dehydration, and sepsis.[2] Mothers of LP infants were found to be more likely to smoke, less likely to place the infants in a supine position for sleep, and less likely to initiate as well as continue breastfeeding. Given the increased risk for morbidity and mortality in this population, greater attention needs to be focused not only on their medical care in the hospital but also on engaging families in providing appropriate home care after discharge.[2,104]

These infants should have closer follow-up during infancy and early childhood with focus on neurodevelopmental and respiratory long-term morbidity.

RSV prophylaxis to this large group is difficult to address with equanimity because of the potential staggering cost of immunizing a relatively low-risk population. It needs, however, to be acknowledged that RSV bronchiolitis can be reduced, and that immunizing LP infants can result in protecting susceptible lungs from extra insult.[95] Clearly, immunizing all LP infants is unrealistic because of cost considerations. There have been attempts to define specific risk factors and identify a subset of LP infants at the highest risk to vaccinate in different countries.[27,105–107] A Canadian study concluded that a risk-scoring tool they developed was a practical, easy-to-use instrument to guide judicious RSV prophylaxis for moderate to high-risk, 33- to 35-weeks' GA infants.[108] To summarize, a policy of selective RSV vaccination of LP infants that is tailored to economic realities should be developed.

SUMMARY

LP infants are born during a "critical developmental time period" for the brain and the lungs and evidence is growing to show that late prematurity is still a time-sensitive, irreversible "decision point" in development. Although these infants are at higher risk for morbidity and mortality compared with term infants, most of them are expected to do well. Yet, the short- and long-term neurodevelopmental and respiratory consequences, other neonatal morbidities, and the emotional and economic burden associated with LP should have practical implication on the approach to and the care of LP infants.

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