Short-Term Outcomes of Infants Born at 35 and 36 Weeks Gestation: We Need to Ask More Questions

Gabriel J. Escobar, MD, † Reese H. Clark, MD, ‡ and John D. Greene, MA *

**BACKGROUND**
Newborns who are 35 to 36 weeks gestation comprise 7.0% of all live births and 58.3% of all premature infants in the United States. They have been studied much less than very low birth weight infants.

**OBJECTIVE**
To examine available data permitting quantification of short-term hospital outcomes among infants born at 35 and 36 weeks gestation.

**DESIGN**
Review of existing published data and, where possible, re-analysis of existing databases or retrospective cohort analyses.

**SETTING**
Multiple hospitals and neonatal intensive care units in the United States and England.

**PATIENTS**
Premature infant cohorts with infants whose dates of birth ranged from 1/1/98 through 6/30/04.

**MAIN OUTCOME MEASURES**
1) Death, 2) respiratory distress requiring some degree of in-hospital respiratory support during the birth hospitalization, and 3) rehospitalization following discharge home after the birth hospitalization.

**RESULTS**
Newborns born at 35 and 36 weeks gestation experienced considerable mortality and morbidity. Approximately 8% required supplemental oxygen support for at least 1 hour, almost 3 times the rate found in infants born at ≥37 weeks. Among 35 to 36 week newborns who progressed to respiratory failure and who survived to 6 hours of age and did not have major congenital anomalies, the mortality rate was 0.8%. Following discharge from the birth hospitalization, 35 to 36 week infants were much more likely to be rehospitalized than term infants, and this increase was evident both within 14 days as well as within 15 to 182 days after discharge. In addition, late preterm infants experienced multiple therapies, few of which have been formally evaluated for safety or efficacy in this gestational age group.

**CONCLUSIONS**
Greater attention needs to be paid to the management of late preterm infants. In addition, it is important to conduct formal evaluations of the therapies and follow-up strategies employed in caring for these infants.

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**KEYWORDS**
neonatal intensive care, outcomes, neonatal, prematurity, moderate prematurity, preterm, preterm birth

Prematurity is the major determinant of neonatal mortality and morbidity. Much of the neonatology literature has focused on outcomes among very low birth weight (VLBW, <1500 g at birth) infants, a group of infants who are usually <33 weeks gestation with the highest rates of mortality and morbidity. Much less is known about premature infants at higher gestations. In 2002, the neonatal mortality rate in term infants in the U.S. was 2.5/1000 live births, 6.9/1000 in babies born at 35 to 36 weeks, 18.5/1000 in babies born at 30 to 34 weeks, and 285.3/1000 among babies <30 weeks. However, since there are so many more babies born at 30 to 36 weeks than at <30 weeks, these infants contribute substantially to the total numbers of neonatal deaths.

It is also known that rates of a number of outcomes (e.g., cerebral palsy,* infection with respiratory syncytial virus, short-term hospital morbidity,* and rehospitalization**-11) in premature infants 30-36 weeks are less than those found in
very premature infants but significantly higher than those found in term infants.

One important subset of these infants is that consisting of newborns born very close to term. No commonly agreed on definition exists as to what constitutes being a “late preterm” infant. One operational criterion that could be employed is a gestational age that is associated with “normal” birth weight (≥2500 g) and that would not warrant automatic admission to a neonatal intensive care unit (NICU). No agreement exists with respect to this, either, although conversations with multiple nursery directors suggest that, in most U.S. hospitals with NICUs, babies <35 weeks gestation are not likely to be admitted to a normal newborn setting. Although this definition appears to have some face validity, it is not based on quantitative data and leaves many questions unanswered (e.g., what happens, or what should happen, to 34 week infants weighing ≥2500 g born at rural hospitals without a NICU?).

In this paper, we examine two problems affecting late preterm infants: respiratory distress and rehospitalization. From the outset, we recognize two important limitations. The first is the absence of a standard definition for “late preterm.” The second is that much of the literature either only focuses on very premature infants or aggregates data on all premature infants into a single category. Thus, we will examine data from studies using several gestational age ranges: eg, 34 to 36, 35 to 36, and 35 to 37 weeks. Our data sources will include recently published studies by us and by others, reanalyzed data from studies using several gestational age ranges. These predictors did not reach significance: maternal age; presence of a maternal problem (chorioamnionitis, abruptio placentae, placenta previa, hypertension, premature rupture of membranes, oligohydramnios, and/or polyhydramnios); gestational age; infant sex; race; small for gestational age status; and four birth weight ranges. These predictors did not reach significance: maternal age, multiple gestation, birth weight, and race. The table shows the substantial impact of decreasing gestation on the likelihood of having any respiratory distress, significant physiologic derangement, or experiencing assisted ventilation. It also shows that the increased risk associated with decreasing gestational age is apparent at 37 weeks. For exam-

### Methods

#### Study Populations

Our study populations consist of cohorts of late preterm infants as reported in recent studies. We restricted ourselves to those studies that (1) did not limit reporting of premature infant outcomes to a single gestational age category (<37 weeks) and (2) permitted some inference as to the outcomes experienced by babies ≥34 weeks gestation. We were also able to re-analyze data from a recently published study so as to isolate the outcomes of late preterm infants. Lastly, we conducted some analyses involving a cohort of 47,495 newborns born between 1/1/02 and 6/30/04 at 6 Kaiser Permanente hospitals with a NICU who met the following criteria: (1) were born in the hospital at the Kaiser Permanente Medical Centers in Hayward, Oakland, Sacramento, San Francisco, Santa Clara, and Walnut Creek; (2) had a gestational age ≥33 weeks; and (3) survived ≥2 hours.

#### Institutional Review Board Approval

All of the studies included in this report were approved by the Institutional Review Boards with jurisdiction over the participating sites and investigators.

### Data Collection

Data collection methods for the cohort of ≥34 week infants with respiratory failure were described in the original report. Data collection methods for the analyses involving the Kaiser Permanente cohort have been described previously.

### Statistical Analysis

We employed logistic regression to conduct the analyses involving the cohort of infants with respiratory failure as well as the analyses involving the occurrence of various forms of respiratory distress in the Kaiser Permanente cohort. For analyses involving rehospitalization in the Kaiser Permanente cohort, we employed Cox proportional hazards models to control for varying lengths of follow-up due to patients leaving the health plan. If a mother had more than one baby in the Kaiser Permanente cohort, we randomly selected only one infant for inclusion in the analyses. We conducted all analyses using SAS.

### Results

#### Respiratory Distress

The most comprehensive analyses of the epidemiology of respiratory distress are the geographically based studies in Sweden, which reported on babies born in the late 1970s and Italy, which reported on babies born in the mid 1990s. Both groups of studies found that the rate of occurrence of any form of respiratory distress increased dramatically among babies born at less than 37 weeks. The results reported by these studies are similar to those found in the analysis of the much more recent Kaiser Permanente cohort. For example, Rubaltelli and coworkers reported the following rates of occurrence of any respiratory distress: 20.6% among babies born at 33 to 34 weeks, 7.3% among 35 to 36 week babies, and 0.6% among babies born at 37 to 42 weeks; in the Kaiser Permanente cohort, these frequencies were 22.1%, 8.3%, and 2.9%, respectively.

Table 1 shows the adjusted odds ratios (AORs) and 95% confidence intervals for statistically significant predictors in multivariate models for the occurrence of three outcomes among the Kaiser Permanente cohort: receipt of supplemental oxygen for ≥1 hour, having a Score for Neonatal Acute Physiology (version II) > 9, or experiencing any form of assisted ventilation. All three models employed the same set of predictors: maternal age; presence of a maternal problem (chorioamnionitis, abruptio placentae, placenta previa, hypertension, premature rupture of membranes, oligohydramnios, and/or polyhydramnios); gestational age; infant sex; race; small for gestational age status; and four birth weight ranges.
ple, compared with babies with gestational ages of 38 to 40 weeks, babies born at 37 weeks were twice as likely to be ventilated, whereas babies born at 36 weeks were five times as likely, and babies born at 35 weeks, nine times as likely.

### Treatment Modalities Experienced by Babies Progressing to Respiratory Failure

Clark and coworkers reported that the three most common diagnoses in newborns with respiratory failure requiring assisted ventilation were respiratory distress syndrome, meconium aspiration syndrome, and pneumonia/sepsis. Among infants 37 to 42 weeks gestation, the frequencies of these three diagnoses were 43%, 9.7%, and 8.3%, respectively. In contrast, among infants 35 to 36 weeks, the frequencies of these diagnoses were 62%, 1.3%, and 8%, respectively.

Among 1011 intubated ventilated late preterm neonates, 864 (85%) received at least one adjunctive therapy (extra fluid volume, surfactant, vasopressors, high frequency ventilation, inhaled nitric oxide, neuromuscular blockade, alkalization, or extracorporeal membrane oxygenation), 521 (52%) received at least 2 of these therapies, and 304 (30%) at least 3. Surfactant was used in 558 (55%) patients, vasopressors in 353 (35%), high-frequency ventilation in 206 (20%), inhaled nitric oxide in 172 (17%), neuromuscular blockade in 167 (17%), alkalosis in 37 (3.6%), and extracorporeal membrane oxygenation in 36 (3.6%).

### Rehospitalization

A small number of studies have reported short-term rehospitalization rates among late preterm infants (ie, within 2-4 weeks of discharge from the birth hospitalization). These studies concur in a number of respects. First, the most common reasons for rehospitalization among late preterm infants are similar to those encountered among term infants: jaundice, feeding difficulties, and/or dehydration. Second, rehospitalization rates are much higher among late preterm infants than in term infants. For example, the rehospitalization rate within 4 weeks in Oddie’s study in England was 2.4% among babies >40 weeks, 3.4% among babies 38 to 40 weeks, and 6.3% among babies 35 to 37 weeks gestation. Third, male infants are more likely to be rehospitalized. Finally, practice variation is widespread, and considerable residual variation across medical centers persists in multivariate models that controlled for many predictors.

However, these studies do not concur in some other respects. For example, Oddie reported that early newborn discharge was protective with respect to rehospitalization. In contrast, in Escobar’s study of NICU graduates, shorter lengths of stay were associated with increased rehospitalization rates among babies 33 to 36 weeks gestation. Escobar and coworkers also found that 34 to 36 week gestation infants who were never in the NICU were much more likely to be rehospitalized than all other infant groups (including babies born at < 34 weeks gestation).

Much less is known about rehospitalization among late preterm infants after the immediate neonatal period, and we were unable to locate published studies permitting disaggregation of outcomes among different subsets of babies <37 weeks. Consequently, we conducted some preliminary analyses looking at rehospitalization within 15 to 182 days after discharge using the Kaiser Permanente cohort. Of the 47,495 babies in the cohort, we established that 26,703 had continuous membership during the first 6 months of life and were...
3.6% among babies was 4.6% and increased as gestational age decreased: it was 1 rehospitalization. The overall crude rehospitalization rate thus eligible for analyses involving the occurrence of at least 1 rehospitalization. The overall crude rehospitalization rate was 4.6% and increased as gestational age decreased: it was 3.6% among babies ≥41 weeks, 4.4% among babies 38 to 40 weeks, 5.6% among babies 37 weeks, 7.3% among babies 36 weeks, 6.8% among babies 35 weeks, 9.1% among babies 34 weeks, and 9.3% among babies 33 weeks gestation.

Table 2 shows the result of a Cox proportional hazards model for the occurrence of at least one rehospitalization between 15 and 182 days following discharge from the birth hospitalization. In this analysis, only the following predictors had significantly elevated hazard ratios: gestational age of 36 weeks (1.67, 95% confidence interval [CI], 1.23–2.25); male sex (1.24, 95% CI, 1.08–1.42); and use of assisted ventilation in the neonatal period (2.04, 95% CI, 1.50–2.79). Gestational age of ≥41 weeks was protective (0.75, 95% CI, 0.61–0.93).

Discussion

It is clear from both the limited literature base as well as from our exploratory analyses that late preterm infants, however defined, experience greater mortality and morbidity than term infants. In the immediate neonatal period, one of the major drivers for increased mortality and morbidity is the presence of various forms of respiratory distress, of which the most common forms are respiratory distress syndrome, pneumonia, and a variety of ill-defined conditions usually lumped under the category known as “transient tachypnea of the newborn.” Meconium aspiration syndrome is less common in late preterm neonates than in term infants.

Our focus on respiratory disorders has been driven by the availability of data and does not mean that these are the only problems encountered by these infants in the immediate neonatal period. Wang and coworkers documented increased rates of other problems in late preterm infants (eg, hypothermia and evaluation for suspected infection).

With respect to respiratory disorders, available data strongly support a number of conclusions. First, although the type of disorders varies, the risk of experiencing respiratory disorders in general rises steeply as gestational age falls below 38 weeks. This increased risk persists even after controlling for infant sex, maternal conditions, multiple gestation, race, birth weight, and small for gestational age status. Given this elevated risk, it is essential that increased research attention be given to the epidemiology of respiratory disorders among infants who are 34 to 37 weeks gestation.

Second, although it is clear that increasing prematurity and severity of illness strongly affect long-term consequences of respiratory disorders, we are in a completely different situation with respect to understanding the role played by specific treatments provided to late preterm neonates with respiratory failure. Use of therapies such as volume expansion, hyperventilation, alkalinization, and paralysis is common. However, none of these therapies has been subjected to a randomized clinical trial, and their safety or efficacy has never been established. Some of these adjunctive therapies (inhaled nitric oxide, high frequency ventilation, and surfactant) have been studied more completely but would benefit from further study, particularly with respect to late preterm infants. It is also important to keep in mind that our data show that, although the use of adjunctive therapies such as inhaled nitric oxide is based on randomized trial data, it is also very common to use other therapies, which have not been properly evaluated, in conjunction with proven therapies. For example, use of alkalinization (by hyperventilation and/or chemical infusion), paralysis, and volume expansion in late preterm infants receiving inhaled nitric oxide is common but has never been studied in randomized trials.

Understanding the effect and safety profile of these “adjunctive” therapies on the outcome and cost of neonatal care is
important. Because of the high costs of research involving newborns with respiratory failure, close attention must be paid to study design, and case-control methods may need to be employed to study some rare outcomes.

Given the substantial proportion of late preterm infants with respiratory disorders and respiratory failure, not to mention the sizeable numbers of these infants, failure to conduct more studies exploring the association between treatments and long-term outcomes (particularly neurodevelopmental ones) would be inexcusable.

With respect to rehospitalization, available data strongly support two conclusions. First, there can be no doubt that late preterm infants are more likely to be rehospitalized than term infants, both immediately after birth hospitalization discharge as well as in the following 6 months. Second, a number of additional predictors also play a role. These include male sex and the occurrence of assisted ventilation in the neonatal period.

However, existing rehospitalization data also raise a number of questions that also merit future study. The first question is: what is the effect of NICU admission on the management and subsequent rehospitalization of late preterm infants? Some of the data from Oddie and coworkers and Escobar and coworkers suggest, but do not prove, that specific follow-up programs are protective. They also suggest that, at least in some cases, admission to the NICU also may be protective. The protective effect of NICU admission on late preterm infants could be occurring in a couple of ways. One possible effect is that, to the extent that NICU staff retains a baby in the NICU through an initial transition period, they may be ensuring that early jaundice and feeding difficulties are identified and treated. NICU staff may also be providing services that are equivalent to those provided by follow-up programs. To fully address this question would require greater knowledge of exactly how these babies are treated in different settings and by different practitioners.

A second question is related to our observations on the heterogeneity of interventions used in late preterm infants with respiratory disorders: are some of these interventions more likely to result in short-, medium-, and long-term consequences that could lead to a need for rehospitalization? If this were the case, the decision to employ such therapies would need to be based on cost-benefit analyses that included postdischarge outcomes, not just in-hospital measures. For example, if it were known that use of paralytic agents was strongly associated with later feeding difficulties, one might design randomized trials comparing paralysis to other sedation approaches. Such trials might include quantification of rehospitalizations and could control for gestational age.

As noted in our introduction, it is very clear that, for many important neonatal outcomes, two important gradients exist. The first is quantitative and is characterized by an exponential decrease in the numbers of babies as gestational age decreases. However, adverse outcomes follow a gradient in the opposite direction, with increasing rates as gestational age decreases. Thus, for certain outcomes, the absolute burden to society may be greater among infants who are not as prema-

ture because there are more such infants. Consideration of these gradients suggests that a broader conceptual shift needs to be made in perinatal epidemiology. Such a shift needs to consider three major issues: (1) in developed nations, it is becoming increasingly common to have more accurate gestational age measures available; (2) when analyzing any dataset, use of cutoffs (particularly dichotomous ones) for continuous data entails loss of information; and (3) given that gestational age gradients exist, and given that previous studies may not have considered the contribution of moderate prematurity to overall outcomes rates, it may be necessary to re-examine certain existing assumptions about the costs and benefits of specific interventions. For example, if one bases certain obstetric interventions only on the outcomes experienced by very low birth weight infants, one may come to erroneous conclusions about the value or risk of such interventions among women presenting with preterm labor and moderate prematurity.

Taken together with our findings, these considerations highlight the need to devote more research attention to late preterm infants and their mothers. Although they do not experience as much morbidity as very premature infants, their numbers are much greater. Key areas for future research include the following:

1. **Prolongation of pregnancy in noninfected mothers**
   The fact that so many late preterm infants require some form of assisted ventilation suggests that assessment of the value of specific obstetric interventions aimed at prolonging pregnancy should take these infants' outcomes into account. For example, not all obstetricians would attempt tocolysis at 33 to 34 weeks gestation.

2. **Specific management strategies**
   In the absence of specific, evidence-based guidelines, which should include rational discharge planning strategies, it is conceivable that both clinicians and insurers may use tacit or "de facto" guidelines that treat these infants based on their birth weight (and/or apparent resemblance to term infants) as well as presumed asymptomatic status. This could lead some infants to be treated, inappropriately, using guidelines defined for term infants. Professional societies such as the American Academy of Pediatrics should take an active role in the definition of gestational age-specific guidelines for late preterm infants.

3. **Support for families**
   Since these infants are perceived as being at low risk, they may not be eligible for specialized programs that have been made available for very premature or very low birth weight infants. In particular, follow-up of these patients in the outpatient clinic should be more frequent with close attention to hydration, degree of hyperbilirubinemia, and development of viral illnesses.

4. **Methodology**
   A greater proportion of neonatal outcome studies should include infants of all gestations so that, when data are analyzed, key predictors (eg, gestational age, birth weight, severity of illness) can be analyzed as continuous variables rather than
using arbitrary cutoffs (e.g., <1500 g). Such study designs might need to incorporate differential sampling fractions for babies of different gestations.

5. Randomized trials
Greater investment in clinical trials that evaluate the safety and efficacy of disease-specific health care interventions for the near to term neonate with significant respiratory failure are urgently needed. Such investment should include efforts to prevent respiratory distress, as has been recently done for term infants born by elective cesarean section.

References

Summary Points
- Available data strongly support the assertion that “late preterm” infants (34 and 36 6/7 week gestation) have higher risks for mortality and morbidity compared with term infants (37 completed weeks through 42 completed weeks).
- Acute respiratory distress is the most common clinical entity seen in late preterm infants. This risk drops sharply beginning at 36 completed weeks of gestation.
- Late preterm infants also experience higher rates of re-hospitalization, both in the immediate postnatal period following initial discharge, as well later in infancy.
- Considerable heterogeneity exists with respect to the management of late preterm infants who have respiratory failure. Many of the interventions used on these infants have not been formally tested.
- Research is needed for strategies to prevent late preterm births, and to optimize their postnatal care.