Persistence of Underweight Status Among Late Preterm Infants

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Objective: To determine the association of late preterm gestation (34-36 weeks’ gestation) with underweight status in infancy.

Design: Retrospective cohort study.


Participants: Seven thousand eight hundred sixty-six infants with gestational ages ranging from 34 to 42 weeks, followed up through the first 18 months of life. Analytic sample consisted of 7624 infants examined at 6 months of age; 7132, at 1 year; and 6957, at 18 months.

Main Exposure: Late preterm (34-36 weeks), early term (37-38 weeks), or full-term (39-42 weeks) gestation.

Main Outcome Measures: Weight-for-age z score of 2 or less at 6, 12, and 18 months.

Results: Compared with full-term gestation, late preterm gestation was associated with increased adjusted odds ratios (AORs) of weight-for-age z score of 2 or less at 6 months (AOR, 3.48 [95% CI, 2.17-5.72]) and 12 months (2.22 [1.07-4.61]). At 18 months, this association was not significant (AOR, 1.62 [95% CI, 0.69-3.84]). After exclusion of infants who were small for their gestational age, late prematurity was associated with underweight status when defined as a decline from birth weight of more than the 10th percentile to a weight-for-age z score of 2 or less at 6 months (AOR, 3.35 [95% CI, 1.76-6.38]) and 12 months (2.72 [1.02-7.27]) but not 18 months (1.88 [0.64-5.55]).

Conclusions: There is an association between late prematurity and underweight status in the first year of life. Further research is needed to determine the effect of this growth pattern on developmental outcomes and to optimize nutritional management.


Recently, awareness has increased of the risk for morbidity and mortality associated with late preterm birth, defined as birth at 34 to 36 weeks’ completed gestation. In the past 2 decades, the US birth rate in this group has increased; late preterm infants now constitute more than 70% of all preterm infants and substantially contribute to the use of health care resources in the neonatal period.1-6 Many studies demonstrate an increased risk for a variety of neonatal complications, including rehospitalization and death in late preterm infants compared with full-term infants.7-10 Evidence also exists that in the first year of life, late preterm infants have a propensity for more severe illness, worse neurodevelopmental outcomes, and higher health care costs.11-16 However, further research is needed to systematically measure outcomes in early childhood for this population, as has been done for infants born at very preterm gestations.

One important outcome for children born preterm is growth and physical development. For late preterm infants, intrauterine growth restriction has been shown to be common, which increases the already high risk for morbidity and mortality.17-19 Late preterm infants may also be more susceptible to feeding difficulties, including breastfeeding failure, which may place them at higher risk for poor weight gain or failure to thrive in early infancy.20,21 However, very few studies to date evaluate the effect of late prematurity on growth outcomes in early childhood after controlling for these factors.

In this study, we analyzed the association of late preterm birth with underweight status at 6, 12, and 18 months of life using electronic health record data from a large pediatric primary care network. We also examined the association of underweight status with early term gestation (37-38 weeks), which has not been previously described. Given the prevalence of late preterm and early term births,
a better characterization of the growth patterns of these children adds to our understanding of the implications of recent birth trends. Such data may also alert pediatric practitioners to the need for closer monitoring of infants who may otherwise be assumed to be at a normal risk for faltering growth.

STUDY POPULATION AND SETTING

We conducted a retrospective cohort analysis of infants born at 34 to 42 weeks’ gestation from January 1 through December 31, 2007. The study was conducted at 31 practices caring for more than 235,000 children and adolescents within The Children’s Hospital of Philadelphia Pediatric Research Consortium, a multistate, hospital-owned, primary care–based research network. Study sites included 4 urban teaching practices, where one-third of children have private insurance, and 26 urban or suburban practices not involved in resident teaching, where most of the children are privately insured. All practices used a commercially available ambulatory electronic health record (EpicCare; Epic Systems Corp) for physician documentation and order entry. The Children’s Hospital of Philadelphia institutional review board approved the study.

Eligible subjects included children in the network who visited practices for well-child care (WCC) within the first 30 days of life and were followed up for at least 18 months. We excluded children with major congenital anomalies and hereditary disorders because their patterns of growth often vary significantly from those of unaffected children. These diagnoses were identified in the chronic problem list for each patient on the basis of codes assigned from the International Classification of Diseases, Ninth Revision, and were clustered into homogeneous categories using a taxonomy previously developed for acute health problems (eTable; http://www.archpediatrics.com).

PREDICTOR AND OUTCOME VARIABLES

The primary aim of this study was to assess the association of underweight status with late preterm birth in this cohort at 6, 12, and 18 months of age using anthropometrical data from the electronic health record. Gestational age was recorded as part of routine care based on available birth hospital discharge records. We categorized infants as late preterm (34–36 completed weeks of gestation), early term (37–38 completed weeks), and full-term (39–42 completed weeks).

In a 2006 review article by Olsen, on specific growth outcomes used to define growth failure, weight-for-age was the predominant choice of indicator with cutoff values primarily at the fifth percentile. We extracted weight data from WCC visits (Current Procedural Terminology codes 99381, 99382, 99391, and 99392) occurring closest to 6 months (range, 4–8 months), 12 months (range, 10–14 months), and 18 months of age (range, 16–20 months), based on the recommended schedule for preventive pediatric care. At each of these intervals, we calculated a z score using the World Health Organization 2006 growth curves, adjusting for the child’s age at measurement, sex, and gestational age. We defined underweight as an attained weight-for-age z score of 2 or less, which represents the cutoff for measurements less than the fifth percentile. As a standardized procedure for preventative visits in each practice site, patient weight was recorded with the patient unclothed using a calibrated, digital scale. We limited observations to preventative visits because children during acute care visits often remain clothed and weights are less likely to be accurate.

In addition to static measurements of attained growth, measurements of growth velocity or slow weight gain have increasingly been used in the literature to define growth failure. Therefore, we also evaluated growth by repeating the analysis after exclusion of infants born small for gestational age (SGA), so that all infants remaining in the sample had a birth weight for gestational age greater than the 10th percentile. We then evaluated which infants experienced a fall in weight-for-age category to less than the fifth percentile at 6, 12, or 18 months of age. This measurement has been used in previous studies as a measure of growth failure.

MODEL BUILDING AND STATISTICAL ANALYSIS

We identified infants born SGA using standard growth curves for birth weight and gestational age developed by Alexander et al. We included these children in our primary analysis because SGA status is often associated with medical indications for late preterm delivery and growth outcomes. Other clinical and demographic covariates to adjust for potential confounding were evaluated on the basis of previous studies of risk factors for inadequate weight gain, including sex, socioeconomic status, and feeding method. We obtained information on delivery method (cesarean vs vaginal) and feeding method (any breastfeeding vs formula only) by searching electronic health record text for documented birth history and visit notes. We also evaluated the contribution of medically significant gastroesophageal reflux disease (prescription of an H2 histamine receptor antagonist or proton pump inhibitor) because evidence suggests that the condition may be associated with differences in growth potential or nutritional intake. To adjust for social and environmental factors, we included patient race (black, white, or other) and insurance status (private insurance at any time during the study vs none). We also approximated annual family income by linking 5-digit zip codes to US Census tract data and grouping them according to the percentage of residents living below the federal poverty level.
We used logistic regression to test the independent association of each potential clinical or demographic covariate with the outcome measure. We then assessed correlation between covariates using bivariate analyses; if 2 variables were collinear, such as insurance type and income, we chose 1 for multivariable analysis to avoid overadjustment bias. We built our base multivariable model and added interaction terms between gestational age and other covariates, such as sex and race. Several factors, including breastfeeding and delivery method, were not significantly associated with the outcome in univariate or multivariable analysis and were removed. No interaction term remained statistically significant after adjustment for multiple testing. Covariates included for the final model were gestational age category, SGA, sex, race, annual family income, and gastroesophageal reflux disease. A secondary analysis excluded SGA infants from the sample. Analyses were performed using commercially available statistical software (STATA, version 11.0; StataCorp).

MISSING DATA

For 581 infants in the study cohort, gestational age data were missing. Because physicians may have been less likely to document gestational age information for full-term infants compared with preterm infants, missing data were likely nonrandom. For regression analyses, we used multiple imputation to impute gestational age for these infants using birth weight, sex, race, insurance status, annual family income, and delivery method. With this technique, we pooled analyses from 5 imputed data sets, adjusting standard errors for missing data uncertainty. Results shown are for the total sample, including infants with imputed gestational age. To confirm results, we also repeated all analyses excluding infants with missing gestational age data; statistical significance and effect sizes did not change (data not shown).

STUDY POPULATION

Of the original data set containing all infants born in the first half of 2007 and seen within the practice network by 30 days of life, 8216 infants were born at 34 to 42 weeks’ gestation and were followed up until at least 18 months of age (Figure). We excluded 350 patients with major congenital or hereditary disorders. Although all remaining 7866 children received care in the practice network through the first 18 months of life, not every child had a documented WCC visit at the recommended ages for preventive pediatric care. Only 7624 had a WCC visit near 6 months of age, 7132 had a WCC visit near 1 year of age, and 6957 had a WCC visit near 18 months (Figure). We conducted \( \chi^2 \) analysis to assess characteristics of children who did not have WCC visits at these age intervals compared with those who did and were included in the analytic sample (Table 1). Overall, children who did not have WCC visits at 6, 12, or 18 months had a similar gestational age distribution compared with children with WCC visits. However, children without WCC visits at 6, 12, or 18 months had a similar gestational age distribution compared with children with WCC visits. However, children without WCC visits were significantly less likely to be white, to be privately insured, or to live in higher income areas. Table 1 depicts the unadjusted association of potential covariates with gestational age category; late preterm infants were signifi-
cantly more likely to be born SGA compared with full-term infants.

UNADJUSTED ANALYSIS

At 6 months of age, 1.6% of infants had an attained weight-for-age \( z \) score of 2 or less. This percentage differed significantly by gestational age, with 4.9% of late preterm infants and 2.5% of early term infants having an attained weight-for-age \( z \) score of 2 or less, compared with 0.9% of full-term infants \((P < .001)\). At 12 months, fewer infants, or 0.9% of the cohort, were underweight by this measure. Differences by gestational age remained significant, with 2.1% of late preterm infants and 1.2% of early term infants meeting this criterion for underweight vs 0.6% of full-term infants \((P = .001)\). At 18 months, the percentage of children with a weight-for-age \( z \) score of 2 or less declined in all groups \((1.4% \text{ of late preterm infants}, 0.9\% \text{ of early term infants}, 0.6\% \text{ of term infants})\). Although underweight status remained more common among late preterm infants compared with full-term infants, the difference was no longer statistically significant.

MULTIVARIABLE ANALYSIS

In multivariable regression analysis, late preterm birth compared with full-term birth was associated with a significantly higher adjusted odds ratio (AOR) of low attained weight-for-age at 6 months \((AOR, 3.48 [95\% CI, 2.17-5.72])\) and 12 months \((2.22 [1.07-4.61])\) \((Table 3\)). At 18 months, this association was not significant \((AOR, 1.62 [95\% CI, 0.69-3.84])\). At 6 months but not 12 or 18 months, birth at 37 to 38 weeks’ gestation was also associated with an increased AOR for low attained weight-for-age \((AOR, 2.02 [95\% CI, 1.32-3.08])\).

### Table 2. Clinical and Demographic Characteristics by Gestational Age Category\(^a\)

<table>
<thead>
<tr>
<th>Gestational Age, No. (% of Infants)</th>
<th>34-36 wk ((n=553))</th>
<th>37-38 wk ((n=1735))</th>
<th>39-42 wk ((n=5336))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>98 (17.7)</td>
<td>236 (13.6)</td>
<td>351 (6.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>273 (49.4)</td>
<td>916 (52.8)</td>
<td>2690 (50.4)</td>
<td>.17</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>271 (49.1)</td>
<td>914 (52.8)</td>
<td>2905 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>195 (35.3)</td>
<td>485 (28.0)</td>
<td>1478 (27.7)</td>
<td>.002</td>
</tr>
<tr>
<td>Other</td>
<td>86 (15.6)</td>
<td>331 (19.1)</td>
<td>944 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Any private insurance</td>
<td>408 (73.8)</td>
<td>1335 (76.9)</td>
<td>4154 (77.8)</td>
<td>.08</td>
</tr>
<tr>
<td>Income below FPL, %(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>213 (38.6)</td>
<td>719 (41.5)</td>
<td>2210 (41.5)</td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>129 (23.4)</td>
<td>437 (25.2)</td>
<td>1382 (25.9)</td>
<td>.19</td>
</tr>
<tr>
<td>10-20</td>
<td>80 (14.5)</td>
<td>211 (12.2)</td>
<td>685 (12.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>130 (23.6)</td>
<td>367 (21.2)</td>
<td>1050 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>305 (55.2)</td>
<td>1045 (60.2)</td>
<td>3587 (67.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any breastfeeding</td>
<td>290 (52.4)</td>
<td>1067 (61.5)</td>
<td>3573 (67.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease(^c)</td>
<td>137 (24.8)</td>
<td>295 (17.0)</td>
<td>734 (13.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: FPL, federal poverty level; SGA, small for gestational age.
\(^a\)Sample sizes and percentages represent the cohort at 6 months of age. The distribution of characteristics in this cohort at 12 and 18 months is similar (see Table 1). Data are unadjusted. Percentages have been rounded and might not total 100. Data for race, FPL, and delivery method categories reflect missing values for some infants. A total of 15 infants had missing information for race, 11 had missing information on zip code, and 261 had missing information on delivery method.
\(^b\)Indicates percentage of zip code residents with incomes below the FPL.
\(^c\)Measured by prescription of at least 1 \(H_2\) histamine receptor antagonist or proton pump inhibitor.

### Table 3. Multivariable Associations of Predictors With Low Attained Weight\(^a\)

<table>
<thead>
<tr>
<th>Weight-for-Age (z) Score ≤2, AOR (95% CI)</th>
<th>6 mo ((n=7624))</th>
<th>12 mo ((n=7132))</th>
<th>18 mo ((n=6957))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34-36</td>
<td>3.48 (2.17-5.72)</td>
<td>2.22 (1.07-4.61)</td>
<td>1.62 (0.69-3.84)</td>
</tr>
<tr>
<td>37-38</td>
<td>2.02 (1.32-3.08)</td>
<td>1.42 (0.80-2.54)</td>
<td>1.25 (0.64-2.41)</td>
</tr>
<tr>
<td>39-42</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>SGA</td>
<td>5.93 (3.97-8.84)</td>
<td>8.52 (4.95-14.66)</td>
<td>7.29 (3.93-13.51)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.89 (1.16-3.07)</td>
<td>1.68 (1.00-2.84)</td>
<td>1.15 (0.65-2.03)</td>
</tr>
<tr>
<td>Female</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.93 (0.53-1.64)</td>
<td>0.46 (0.21-1.03)</td>
<td>0.91 (0.38-2.15)</td>
</tr>
<tr>
<td>Other</td>
<td>1.11 (0.65-1.88)</td>
<td>0.87 (0.44-1.73)</td>
<td>1.27 (0.60-2.66)</td>
</tr>
<tr>
<td>White</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Income below FPL, %(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>2.09 (1.13-3.86)</td>
<td>1.89 (0.83-4.31)</td>
<td>1.29 (0.49-3.40)</td>
</tr>
<tr>
<td>5-10</td>
<td>1.25 (0.66-2.35)</td>
<td>1.39 (0.62-3.15)</td>
<td>1.38 (0.55-3.46)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>0.83 (0.49-1.43)</td>
<td>0.73 (0.36-1.49)</td>
<td>1.06 (0.50-2.23)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease(^c)</td>
<td>2.00 (1.27-3.15)</td>
<td>1.28 (0.69-2.40)</td>
<td>1.35 (0.68-2.71)</td>
</tr>
</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; FPL, federal poverty level; SGA, small for gestational age.
\(^a\)Outcome defined as attained weight-for-age \(z\) score of 2 or less.
\(^b\)Indicates percentage of zip code residents with incomes below the FPL.
\(^c\)Measured by prescription of at least 1 \(H_2\) histamine receptor antagonist or proton pump inhibitor.
status through 18 months of age. We did not demonstrate any interaction effect between gestational age and SGA.

After exclusion of SGA infants, we also demonstrated an association between late preterm birth and inadequate weight gain when defined as a decline from a birth weight greater than the 10th percentile to a weight-for-age z score of 2 or less (Table 4). Compared with full-term infants, late preterm infants had AORs of 3.35 (95% CI, 1.76-6.38) at 6 months and 2.72 (1.02-7.27) at 12 months for inadequate weight gain; at 18 months, this trend persists but does not reach statistical significance (1.88 [0.64-5.55]).

Our study demonstrates that children born late preterm are at increased risk for underweight status (specified as attained weight less than the fifth percentile) at 6 and 12 months; this trend persists at 18 months but does not reach statistical significance. Our findings support an association of this outcome with late prematurity independent of SGA status, which itself is a strong predictor of being underweight at 6, 12, and 18 months. For late preterm infants with birth weights greater than the 10th percentile who may otherwise be assumed to be “normal,” pediatricians should be attentive to the increased risk for inadequate weight gain beyond the neonatal period.

Many studies have systematically measured growth in early childhood for very preterm infants with and without SGA.44-48 However, most of the literature on the physical development of late preterm infants focuses on intrauterine or immediate postnatal growth. As a common complication of late preterm births, intrauterine growth restriction significantly increases the risk for several complications in this population, including mortality in the first year of life.17,19

Few studies evaluate early childhood physical growth outcomes of late preterm children.9 One population-based cohort study of 3285 term and late preterm infants born in southern Brazil demonstrates an increased risk for underweight (weight-for-age z score, ≤2) and growth stunting (length-for-age z score, ≤2) in late preterm compared with full-term children at 12 and 24 months.49 In a US study, Gyamfi50 reports no significant difference in height and weight percentiles between 145 late preterm and full-term children at a median age of 48 (range, 32-64) months, with similar results after adjustment for patient race; the author notes, however, that further validation of this finding is warranted with a larger sample size. Our study extends the literature on outcomes of late prematurity by evaluating childhood growth in a large primary care cohort of infants in the United States, adjusting for a variety of clinical and social factors that may contribute to weight status.

Our finding that at 6 months, infants born at 37 to 38 weeks' gestation are also at increased risk for underweight status compared with infants born at later term gestation adds new information; this finding is consistent with previous studies documenting a dose effect of lower gestations on a range of other outcomes.1,17,51,52 The results are of particular interest given recent epidemiologic trends in gestational length for US births. Since 1990, the distribution of gestational age has shifted downward, with an increase in the proportion of births at 37 to 39 and 34 to 36 weeks' gestation.53 Given that late preterm and early term deliveries together constitute more than one-third of US births, or roughly 1.5 million deliveries, a 2-fold increase in the odds of faltering growth for these infant groups bears a significant health impact at a population level.54

Our findings may also be significant given the increased awareness of cognitive and neurodevelopmental outcomes associated with late prematurity. Studies have demonstrated increased risk for developmental delay, lower IQ, lower school performance, and cerebral palsy in late preterm children compared with full-term children.11,13,15,16 Although the contribution of inadequate weight gain to cognitive outcomes for this population has not been described, previous studies suggest that failure to thrive in infancy may be associated with adverse cognitive and developmental outcomes.49,55,56 However, the risks of underweight status must also be balanced against evidence suggesting that early rapid weight gain in low-birth-weight infants is associated with increased risk for childhood or adult obesity.57,58 Parents and clinicians should be attentive to the increased risk for underweight status and the potential effect of growth patterns on later childhood health and development for late preterm infants.
This study has several limitations, primarily related to the observational study design and absence of randomization. We lacked data on certain prenatal and postnatal risk factors, including parental size and maternal smoking. Although more detailed information on obstetric and neonatal history, including indication for delivery, was available for some infants, these data were inconsistently documented and therefore not reliable for analysis. Although unobserved factors may have influenced selection into gestational age groups and biased the results, the large AORs make these unmeasured variables less likely to account for observed differences between groups. In addition, because this study was retrospective, we considered measurements of infant length and head circumference as less reliable than weight and therefore did not use them for the primary analysis. Although weight-for-length is often considered to be a more specific indicator of acute risk compared with weight-for-age, weight-for-age remains the most common indicator used in previous studies of growth failure. Finally, our ability to characterize infant feeding was limited owing to a lack of systematic documentation. We could not ascertain the extent of formula supplementation for breastfed infants, which may contribute to the lack of statistical significance for this variable. These limitations are balanced by the following multiple strengths: a long follow-up period with growth measured at multiple ages, the ability to adjust for a variety of potentially confounding variables, and the racial and socioeconomic diversity of the cohort, which increases the generalizability of results.

CONCLUSIONS

In 2009, more than 357 000 infants born in the United States were late preterm, a group that constitutes 70% of all preterm births. Systematic measurement of early childhood outcomes for this population is important to understanding the epidemiologic impact of recent birth trends. We demonstrate an association between late preterm and underweight status in the first 12 months in a large primary care cohort. Although SGA is a common complication of late preterm birth and a strong predictor of later growth outcomes, we demonstrate that birth at late preterm and low end of normal gestations is an independent risk factor for underweight status in infancy. Further research is needed to validate and extend our findings and to determine the effect of this growth pattern on developmental outcomes and to optimize nutritional management in these children.

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Author Contributions: Dr Goyal had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Goyal, Fiks, and Lorch. Acquisition of data: Goyal and Lorch. Analysis and interpretation of data: Goyal, Fiks, and Lorch. Drafting of the manuscript: Goyal and Fiks. Critical revision of the manuscript for important intellectual content: Goyal, Fiks, and Lorch. Statistical analysis: Goyal and Fiks. Obtained funding: Lorch. Administrative, technical, and material support: Goyal and Fiks. Study supervision: Lorch.

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