Adverse Neonatal Outcomes Associated With Early-Term Birth

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IMPORANCE Full-term neonates born between 37 and 41 weeks’ gestational age have been considered a homogeneous, low-risk group. However, recent evidence from studies based on mode of delivery has pointed toward increased morbidity associated with early-term cesarean section births (37-38 weeks) compared with term neonates (39-41 weeks).

OBJECTIVE To compare the short-term morbidity of early-term vs term neonates in a county-based birth cohort using the primary objective of admission to a neonatal intensive care unit (NICU) or neonatology service.

DESIGN, SETTING, AND PARTICIPANTS Retrospective population-based 3-year birth cohort study (January 1, 2006–December 31, 2008) at all major birth hospitals in Erie County, New York. All full-term live births comprised the birth cohort; this information was obtained from the hospitals’ perinatal databases, and data pertaining to NICU or neonatology service admissions were extracted from individual medical records.

EXPOSURE Gestational age of early term (370/7-386/7 weeks) vs term (390/7-410/7 weeks).

MAIN OUTCOMES AND MEASURES Admission to the NICU or neonatology service.

RESULTS There were 33 488 live births during the 3-year period, of which 29 741 had a gestational age between 37 and 41 weeks. Of all live births, 9031 (27.0%) were early term. Compared with term infants, early-term neonates had significantly higher risks for the following: hypoglycemia (4.9% vs 2.5%; adjusted odds ratio [OR], 1.92), NICU or neonatology service admission (8.8% vs 5.3%; adjusted OR, 1.64), need for respiratory support (2.0% vs 1.1%; adjusted OR, 1.93), requirement for intravenous fluids (7.5% vs 4.4%; adjusted OR, 1.68), treatment with intravenous antibiotics (2.6% vs 1.6%; adjusted OR, 1.62), and mechanical ventilation or intubation (0.6% vs 0.1%; adjusted OR, 4.57). Delivery by cesarean section was common among early-term births (38.4%) and increased the risk for NICU or neonatology service admission (12.2%) and morbidity (7.5%) compared with term births. Among vaginal deliveries, early-term neonates (6.8%) had a significantly higher rate of NICU or neonatology service admission compared with term neonates (4.4%).

CONCLUSIONS AND RELEVANCE Early-term births are associated with high neonatal morbidity and with NICU or neonatology service admission. Evaluation of local prevalence data will assist in implementation of specific preventive measures and plans, as well as prioritize limited health care resources.
Term pregnancy has been defined as one in which 37 to 41\(^{6/7}\) weeks have elapsed since the first day of the last menstrual period, referred to as postmenstrual age (PMA).

Neonates born during this 5-week period have traditionally been considered a homogeneous low-risk group. Categorizing groups of newborns is of value to focus attention on negative outcomes and to develop strategies to address the causes. For example, the late-preterm neonate emerged as a newly described group in the last decade, defined in part to draw attention to the significantly higher than perceived risk for morbidity and mortality. This resulted in efforts such as the 2005 workshop of the Eunice Kennedy Shriver National Institute of Child Health and Human Development on late-preterm infants (34-36\(^{6/7}\) weeks’ PMA), which served as a platform for raising awareness and effecting prevention.

The designation of early-term infants (37-38\(^{6/7}\) weeks’ PMA) was more recently coined to focus attention on the risk for morbidity and mortality in such infants compared with other term infants born at 39 to 41\(^{6/7}\) weeks’ gestational age. Morbidity among early-term infants is considerably less than that among late-preterm infants. However, early-term infants outnumber late-preterm infants by 3 to 1 in the United States (27.6\% vs 8.7\% of all births in 2009). Studies linking gestational age to outcomes among term neonates have focused on the presence of labor and mode of delivery and have provided limited description of neonatal outcomes or are based on admissions to a tertiary care center and not a specific geographic area.

The objectives of this study were to determine the effect of gestational age at birth for all full-term neonates born within Erie County, New York, as an independent factor responsible for neonatal morbidity and to highlight any differential morbidity between early-term and term neonates. We hypothesized that neonates born between 37\(^{6/7}\) and 38\(^{6/7}\) weeks’ PMA (early-term neonates) compared with those born between 39\(^{6/7}\) and 41\(^{6/7}\) weeks’ PMA (term neonates) would have greater neonatal morbidity and higher admission rates to a neonatal intensive care unit (NICU) or neonatology service (NS) irrespective of mode of delivery. To our knowledge, this is the first population-based, countywide assessment of neonatal morbidity among early-term infants based on individual medical record analysis in the United States.

Methods

The study was approved by the institutional review board at each participating institution. Between January 1, 2006, and December 31, 2008, the study was conducted in a population-based cohort consisting of all full-term live births within Erie County, New York. For his study, we used the following definitions: neonates with early-term birth (born between 37\(^{6/7}\) and 38\(^{6/7}\) weeks’ PMA), neonates with term birth (born between 39\(^{6/7}\) and 41\(^{6/7}\) weeks’ PMA), and neonates with full-term birth (born between 37\(^{6/7}\) and 41\(^{6/7}\) weeks’ PMA).

Erie County has 4 birth hospitals, comprising 2 level III facilities (one of which houses the Regional Perinatal Center) and 1 each with a level I and level II nursery. The perinatal databases for each facility was used for information about all live births. In decreasing order of preference, gestational age was determined by early ultrasonography, the last menstrual period, or postnatal clinical examination results.

The list of all full-term neonates requiring admission to the NICU or transfer to the NS in the case of a level I facility was determined from the neonatology logbook or database at each facility. Further information about such admissions was extracted from a review of individual medical records, databases, and logbooks.

Maternal and Neonatal Characteristics

Pertinent baseline maternal and neonatal characteristics were extracted from individual medical records for all neonates admitted to the NICU or NS. Information extracted from each hospital’s perinatal database for term neonates not admitted to the NS included the following: prenatal care, maternal age, mode of delivery, maternal marital status, and self-reported maternal race/ethnicity.

Outcome Measures

The primary outcome measure was admission to the NICU or NS. The secondary outcome measures included respiratory morbidity, duration of hospital stay, need for administration of intravenous fluids, and requirement for intravenous antibiotic therapy. For this study, we defined respiratory morbidity as any form of respiratory distress that necessitated admission of the neonate to the NICU or NS irrespective of the need for any diagnostic tests or therapeutic intervention. In contrast, respiratory support included the entire spectrum ranging from nasal cannula and oxygen hood to mechanical ventilation. We further identified isolated cases that required surfactant use, inhaled nitric oxide, high-frequency ventilation, mechanical ventilation or intubation, or extracorporeal membrane oxygenation.

Indications for intravenous fluids included any primary gastrointestinal pathologic condition or a nutrition-related disorder, such as feeding intolerance or hypoglycemia. Neonates who needed intravenous fluids for their respiratory or neurological status were also included. Neonates were excluded if they had been born in a different county and were transported for admission to the referral NICU or if they had congenital anomalies or malformations (eg, gastroschisis, diaphragmatic hernia, chromosomal anomalies, complex congenital heart disease, and others) that would require NICU admission for an underlying condition-related intervention irrespective of gestational age. The need for intravenous antibiotics was defined as administration of antibiotics by intravenous route for any indication, including suspected sepsis.

Statistical Analysis

Qualitative variables were expressed as percentages, and bivariate analyses were performed using the \(\chi^2\) test or Fisher exact test. Continuous variables, distributed normally, were presented as means (SDs) and were compared using \(t\) test. For skewed data, continuous variables were reported as medians (interquartile ranges) and were compared using the Wilcoxon rank sum test.
The primary and secondary outcome measures were binary; therefore, a logistic regression model was used to calculate the odds ratio (OR). The final results were expressed as ORs (95% CIs). The factors adjusted for included sex, prenatal care, maternal age, mode of delivery, and self-reported maternal race/ethnicity. These outcomes were expressed as adjusted ORs.

After obtaining information from the databases and the medical record reviews, the 2 sources were merged using a unique patient identifier based on the medical record numbers. All analyses were performed using statistical software (STATA, version 11.0; StataCorp LP).

Results

There were 33,488 live births in Erie County, New York, during the 3-year study period. Among all live births, 29,741 had a gestational age between 37 and 416/7 weeks. In 68.6% of these births, gestational age was determined by first-trimester ultrasonography, which was almost equally distributed between the early-term neonates (68.6%) and the term neonates (69.2%). Although 99.5% of women received some form of prenatal care, data about the month of prenatal care initiation was missing in 7.9% of all deliveries. In the remainder of deliveries, gestational age was determined based on the last menstrual period; when that information was unavailable or was inconsistent with a neonate’s examination findings, gestational age was based on postnatal clinical examination results.

Of all full-term neonates, 77 (0.2% of all live births) were excluded because of congenital malformations that would have automatically required NICU admission; therefore, 29,664 neonates constituted the final study population (Figure 1). The births were almost equally distributed across the 4 facilities, with the most occurring at the Regional Perinatal Center. Of all 33,488 live births, 27.0% were early-term neonates, and 61.6% were term neonates.

The stillbirth rates were 2.0 per 1000 at 37 to 38 weeks’ gestational age and 0.8 per 1000 at 39 to 41 weeks’ gestational age. There were 8 deaths (0.09%) among the early-term neonates and 9 deaths (0.04%) among the term neonates during the neonatal period.

The baseline maternal and neonatal characteristics are given in Table 1 and Table 2, respectively. Mothers delivering early-term infants were slightly older and were more likely to be married compared with mothers delivering term infants. As expected, the term neonates weighed significantly more than the early-term neonates. Early-term neonates were also more
likely to be male than term neonates. No significant differences were noted between the 2 groups for Apgar scores of 5 or less at 1 and 5 minutes.

There was a significant difference in mode of delivery between the 2 groups, with 38.4% of early-term neonates being born via cesarean section compared with 29.3% of term neonates. Conversely, approximately 37% of all cesarean section full-term deliveries (37-41 6/7 weeks) were performed in the early-term gestational age range (37-38 6/7 weeks’ PMA).

Admission temperature and selected laboratory results from early-term and term infants are given in Table 3. These findings are derived from smaller subsets of neonates because the information was unavailable on all births. Early-term neonates had a slightly higher cord pH compared with term neonates. The lowest recorded blood glucose level was significantly lower for early-term neonates. However, the admission temperatures and complete blood cell counts were similar between the 2 groups.

Significantly more early-term neonates (8.8%) required NICU admission or admission to the NS compared with term infants (5.3%) (Table 4). Although the total duration of hospital stay (including the healthy newborn nursery and the NICU) seemed comparable between the 2 groups, significantly more early-term neonates compared with term neonates had a hospital stay of at least 5 days.

Early-term infants were at higher risk for the following: hypoglycemia, need for respiratory support, requirement for surfactant use, and need for IV antibiotic therapy. Significant differences were noted for admission to the NICU or NS, respiratory distress, mechanical ventilation or intubation, primary diagnosis of hypoglycemia, need for IV fluids, and need for IV antibiotic therapy.

### Table 2. Baseline Neonatal Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early-Term Neonates&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Term Neonates&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>52.1</td>
<td>50.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR, g</td>
<td>3204 (2913-3515)</td>
<td>3487 (3204-3771)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥2500 g, %</td>
<td>94.5</td>
<td>99.2</td>
<td></td>
</tr>
<tr>
<td>&lt;2500 g, %</td>
<td>5.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Small for gestational age, %&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.4</td>
<td>5.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Large for gestational age, %&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11.7</td>
<td>7.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Apgar score of ≤5, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 min</td>
<td>1.3</td>
<td>1.5</td>
<td>.41</td>
</tr>
<tr>
<td>At 5 min</td>
<td>0.1</td>
<td>0.1</td>
<td>.89</td>
</tr>
</tbody>
</table>

### Table 3. Admission Temperature and Other Laboratory Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Neonates</th>
<th>Median (IQR)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord pH</td>
<td>960</td>
<td>7.27 (7.27-7.32)</td>
<td>.02</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>1732</td>
<td>53 (48-58)</td>
<td>.24</td>
</tr>
<tr>
<td>Platelet count, ×10&lt;sup&gt;3&lt;/sup&gt;/μL</td>
<td>1510</td>
<td>248 (186-201)</td>
<td>.73</td>
</tr>
<tr>
<td>White blood cell count, /μL</td>
<td>725</td>
<td>17 800 (13 100-22 400)</td>
<td>.02</td>
</tr>
<tr>
<td>Admission temperature, °C</td>
<td>1613</td>
<td>36.8 (36.6-37.0)</td>
<td>.45</td>
</tr>
<tr>
<td>Lowest blood glucose level, mg/dL</td>
<td>1610</td>
<td>43 (29-56)</td>
<td>.02</td>
</tr>
</tbody>
</table>

### Table 4. Multivariate Logistic Regression Comparing Morbidities Between Early-Term Neonates and Term Neonates

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to the NICU or NS</td>
<td>798 (8.8)</td>
<td>1.72 (1.57-1.89)</td>
</tr>
<tr>
<td>Duration of hospital stay ≥5 d</td>
<td>175 (1.9)</td>
<td>1.69 (1.39-2.06)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>492 (5.4)</td>
<td>1.66 (1.47-1.87)</td>
</tr>
<tr>
<td>Support*</td>
<td>182 (2.0)</td>
<td>1.88 (1.54-2.29)</td>
</tr>
<tr>
<td>Mechanical ventilation or intubation</td>
<td>58 (0.6)</td>
<td>4.93 (3.12-7.79)</td>
</tr>
<tr>
<td>Surfactant use</td>
<td>31 (0.3)</td>
<td>7.10 (3.48-14.49)</td>
</tr>
<tr>
<td>Primary diagnosis of hypoglycemia</td>
<td>440 (4.9)</td>
<td>2.01 (1.76-2.29)</td>
</tr>
<tr>
<td>Need for IV fluids</td>
<td>680 (7.5)</td>
<td>1.78 (1.61-1.97)</td>
</tr>
<tr>
<td>Need for IV antibiotic therapy</td>
<td>234 (2.6)</td>
<td>1.60 (1.36-1.90)</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; NICU, neonatal intensive care unit; NS, neonatology service.

<sup>a</sup>Postmenstrual age of 37 to 38 6/7 weeks.

<sup>b</sup>Postmenstrual age of 39 to 41 6/7 weeks.

<sup>c</sup>Birth weight at or below the 10th percentile according to growth curves by Fenton.

<sup>d</sup>Birth weight at or below the 90th percentile according to growth curves by Fenton.

<sup>e</sup>Using Wilcoxon rank sum test.
for intravenous fluids, treatment with intravenous antibiotics, mechanical ventilation or intubation, surfactant use, and respiratory morbidity (Table 4). These differences persisted after adjusting for sex, birth weight, mode of delivery, maternal age, and self-reported maternal race/ethnicity in a multivariate logistic regression model. Among early-term infants at the Regional Perinatal Center (the only NICU in the county with advanced respiratory support, such as nitric oxide or extracorporeal membrane oxygenation), 10 patients received high-frequency ventilation for noncongenital conditions (excluding diaphragmatic hernia, congenital heart disease, and others), 4 patients required inhaled nitric oxide, and 1 patient needed extracorporeal membrane oxygenation. Among term infants, 10 patients required high-frequency ventilation, 5 patients needed inhaled nitric oxide, and 2 patients received extracorporeal membrane oxygenation. The need for inhaled nitric oxide was higher among early-term neonates (0.44 vs 0.24 per 1000 live births).

To evaluate the effect of cesarean section on neonatal morbidity, we analyzed the morbidities associated with each gestational age (in weeks) based on mode of delivery. An inverse relationship among the NICU admission rate (Figure 2), respiratory morbidity and the need for intubation (Figure 3), and gestational age for both vaginal and cesarean section deliveries was noted for early-term births. The additive effect of cesarean section delivery on the need for admission to an NS and respiratory morbidity was also highest at a younger gestational age (Figures 2 and 3).

Overall, delivery by cesarean section increased the risk for NICU or neonatology service admission (12.2%) and morbidity (7.5%) compared with term births. Even among vaginal deliveries, early-term neonates (6.8%) had a significantly higher rate of NICU or neonatology service admission compared with term neonates (4.4%).

Discussion

There are approximately 4.13 million births every year in the United States. Of these, 27.6% are at early-term gestational age, resulting in approximately 1,140,000 early-term neonates in the United States. During the study period (2006–2008), 185,495 early-term births occurred in New York State, accounting for about 25% of all births and similar to the 27.0% reported in our study, suggesting that our population is representative of state and national data. Similar to national data, early-term births accounted for more than 3 times the number of late-preterm births in Erie County, New York (9031 vs 2404) (Figure 1).

Although we observed statistically significant differences in maternal characteristics, such as age, marital status, race/ethnicity, and insurance coverage, the clinical significance of these differences is unclear (Table 1). Significantly more early-term infants were delivered by cesarean section compared with term infants, which is a contributor to longer duration of hospital stay and more respiratory morbidity in this population. Previous studies have focused on mode of delivery as a cause of morbidity in full-term neonates. It is well established that elective cesarean section delivery, especially in the absence of labor, is a strong predictor of neonatal morbidity. This study demonstrates that gestational age remains a strong predictor of neonatal morbidity even after adjustment for mode of delivery, as well as other common prognostic factors (Table 4).

Most early-term infants (94.5%) weighed at least 2500 g at birth and had normal Apgar scores and cord pH similar to those in term infants (Table 2) and appeared mature, providing false assurance to the clinical provider and parents. However, these neonates were physiologically immature as evidenced by significantly lower birth glucose levels, often necessitating intravenous fluid administration and greater need.
for respiratory support, surfactant use, and mechanical ventilation or intubation, resulting in an increased risk for admission to the NICU or neonatology service (Table 4). The need for mechanical ventilation or intubation was 6-fold higher and the requirement for surfactant use was 7-fold higher in early-term neonates compared with their term counterparts.

More early-term neonates than term neonates were classified as small for gestational age and as large for gestational age (Table 2). The percentages of infants small for gestational age (6.4%) and infants large for gestational age (11.7%) were significantly higher for the early-term group. The classification of small for gestational age and large for gestational age was based on growth curves by Fenton.14

Increasing awareness about early-term elective inductions, ever-rising cesarean section delivery rates, and continued low rates of vaginal births after cesarean section (despite American College of Obstetrics and Gynecology recommendations27), along with the morbidity associated with early-term births, has spurred interest in the reduction of early-term deliveries.9,12 A novel method of addressing these issues is to include them as a part of quality initiatives. Two notable examples are the Ohio Perinatal Quality Collaborative18 and the Utah Women and Newborn Clinical Integration Program.19 Such initiatives will also raise awareness among women who perceive early-term deliveries as being safe.20

Our study had several limitations. We were unable to perform a detailed analysis of maternal factors and obstetric indications for early-term deliveries. Hence, we could not categorize these deliveries into spontaneous and indicated categories.21 It is possible that the reason for the early-term delivery (eg, fetal distress) could have been responsible, in turn, for the observed increase in morbidity, resulting in confounding by indication. Our inability to obtain data about the indications for the deliveries makes it impossible to discern the contribution of gestational age as a factor independent of the indication for an early delivery.

In the case of cord pH, hematocrit, and complete blood cell counts, the results were obtained from small subsets of the original cohort. In turn, this was due to fewer neonates requiring these tests based on clinical indications, as well as missing data. Both of these factors could lead to ascertainment bias.

The study also had limitations associated with the retrospective design in collecting data. The most prominent of these is probably associated with the determination of gestational age. While, prospectively, it is possible to use a priori-defined criteria to determine gestational age, the same is not possible retrospectively. In our study, gestational age was determined in approximately 70% of neonates by first-trimester ultrasonography, which is the current gold standard. Even with highly statistically significant results, because gestational age categories are the main focus of this study, the inability to precisely determine gestational age for the remaining 30% poses certain limitations to the interpretation of the results.

The effect of preventing early-term births on the incidence of stillbirths remains an area of controversy.22 In the absence of high-quality randomized trials, we have to ascertain this association from preintervention and postintervention studies.23-26 Some evidence has demonstrated an increase in macrosomia and the likelihood of stillbirth at 37 to 38 weeks’ gestational age following implementation of policies to prevent elective early-term deliveries.27 A 2012 study28 from Scotland reported an association between elective induction of labor and reduced extended perinatal mortality in infants delivered between 37 and 41 weeks’ gestational age. In contrast, the aforementioned study19 from Utah reported a decrease in the incidence of stillbirths at 37 and 38 weeks’ gestational age following implementation of a policy discouraging early-term elective deliveries. Physicians and hospitals implementing policies to prevent elective induction at 37 to 38 weeks’ gestational age must be aware of the conflicting results about the rate of stillbirth at early term. A well-designed randomized controlled trial, with adequate power to demonstrate whether prohibiting elective induction increases the rate of stillbirth, is warranted to address this controversy.22

Although long-term follow-up assessment of these children was beyond the scope and design of the present study, some longitudinal studies27,28 are beginning to propose that the effects of earlier birth might have long-term consequences on academic performance and development. A notable future direction would be to perform cost-effectiveness analyses of the maternal-infant dyad associated with early-term births, which can account for longitudinal effects, such as the effect of prior cesarean sections on future obstetric decision making.

We conclude that early-term delivery is associated with greater morbidity and with increased admission to the NICU or neonatology service in a geographic area-based setting. This increased risk is more profound with cesarean section deliveries but exists for vaginal deliveries as well. There is a continuous relationship between gestational age and neonatal morbidity from early pregnancy onward, with a nadir at about 39 weeks.1 Evaluation of local prevalence data will assist in implementation of specific preventive measures and plans, as well as prioritize limited health care resources.

Targeted obstetric practices and maternal education aimed at reducing early-term deliveries (similar to the Eunice Kennedy Shriver National Institute of Child Health and Human Development effort to reduce late-preterm deliveries) will have a significant influence on health care costs by reducing NICU admissions. Further research on maternal factors leading to early-term delivery and its financial effect is required to improve outcomes in the early-term neonatal population.
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Original Investigation Research
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REFERENCES


