Lower respiratory tract disorder hospitalizations among children born via elective early-term delivery

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Abstract

Objective: We evaluated the hypothesis that elective early-term delivery increases the risk of childhood lower respiratory tract disorder hospitalization.

Methods: Children born via early-term elective inductions were compared to full- or late-term elective inductions in a retrospective cohort study using Washington State birth certificate and hospital discharge data. Outcomes were the odds of lower respiratory disorder hospitalization before age five and cause specific odds ratios for asthma, bronchiolitis, bronchitis, and pneumonia. In addition, a subgroup analysis excluding infants with perinatal complications was conducted.

Results: Electively induced early-term children were at significantly increased risk of hospitalization before age five for lower respiratory disorders compared to similar full- or late-term children (adjusted OR: 1.31, 95% CI: 1.11–1.55). Bronchiolitis was the only cause-specific outcome with a statistically significant increase in odds of hospitalization, though comparable increases were found for the less common diagnoses of asthma (adjusted OR: 1.39, 95% CI: 0.93–2.08) and pneumonia (adjusted OR: 1.27, 95% CI: 0.99–1.64). Excluding infants with perinatal complications did not alter the results.

Conclusions: There was an association between electively induced early-term delivery and hospitalization for lower respiratory tract disorders before age five. This reinforces policies discouraging elective early-term delivery.

Keywords

Asthma, bronchiolitis, bronchitis, gestational age, pneumonia

Introduction

Historically, infants born between 37 and 42 weeks were considered term and at equal risk of poor birth outcomes. However, recent studies demonstrate an increased risk of neonatal morbidity and mortality among infants born at early-term (37–38 weeks gestation) compared to full- or late-term (39–41 weeks gestation) [1–3]. Similarly, infants born late-preterm (34–36 weeks gestation) are at increased risk of immediate neonatal morbidity and mortality [4–6]. However, less information is available regarding the long-term complications in children born early-term, warranting further investigation.

The primary objective of this study was to use birth certificate and hospital discharge data from Washington State to evaluate the hypothesis that children born via elective early-term delivery are at an increased risk of hospitalization due to lower respiratory tract disorders before age five. Second, we assessed the strength of this relationship in infants with no apparent respiratory complications at postnatal discharge. This subgroup analysis examined the possibility of subclinical pathology that predisposes children to lower respiratory disorders in childhood.

Methods

Design

We conducted a population-based retrospective cohort study with birth certificate data in Washington State from 2003 to 2008. These birth certificate data were linked to hospital inpatient discharge reports available from Washington State’s Comprehensive Hospital Abstract Reporting System (CHARS) for 2003–2013 [7].

Measures

Singleton infants born at gestational ages of 37–41 weeks were randomly selected from all births in Washington State between 2003 and 2008 and frequency matched by birth year with a ratio of three to one, unexposed to exposed, before the
inclusion and exclusion criteria were applied. The unexposed group was comprised of children born full- or late-term (39–41 weeks gestation) and the exposed group was comprised of children born early-term (37–38 weeks gestation). Gestational age was defined using birth certificate data. To minimize misclassification, only children with a concordant gestational age by best clinical estimate and by last menstrual period within one week were selected.

We included only those deliveries that were induced without medical indication. Birth certificate and the maternal CHARS records were combined to identify induced deliveries. Merging birth certificate and CHARS records has been previously validated in Washington State as an effective method of addressing the underreporting common in birth certificate data [8]. Maternal and fetal indications for early-term delivery were identified using The Joint Commission’s guidance on indications for early-term delivery [9] and expanded upon using birth certificate and/or CHARS data. Specific diagnoses and codes for both induced and indicated variables are available in Appendix 1. In addition, infants with implausible birth weights for their gestational age (<2000 g or >6500) were excluded.

The primary outcome of interest was lower respiratory tract diagnoses severe enough to warrant hospital admission before age five. These conditions included asthma (ICD-9: 493), bronchiolitis (ICD-9: 466.1), bronchitis (ICD-9: 490), and pneumonia (ICD-9: 480–488). A case was a child admitted one or more times for any of the diagnoses of interest. A priori confounding factors available from the birth certificate included maternal age (years), maternal race (white, black, Hispanic, Asian, Native American, other), any smoking during pregnancy (yes, no), parity (continuous), and maternal hospital bill payer (private insurance, public insurance or charity) as a proxy for socio-economic status.

Based on early-term versus full- or late-term exposure status, we assessed maternal and pregnancy characteristics, number of respiratory hospitalizations by gestational age measured in weeks, and odds of respiratory hospitalization before age five for a lower respiratory tract disorder. We calculated an unadjusted and adjusted odds ratio (aOR) for lower respiratory tract disorder hospitalizations and associated 95% confidence intervals using logistic regression. We also determined the cause-specific odds ratios for each of the four respiratory diagnoses. In the cause-specific analysis, we limited asthma diagnoses to children older than 2 years old and bronchiolitis diagnoses to younger than 2 years old to address possible misclassification between these diagnoses. The age cut-offs were based on the American Academy of Pediatrics bronchiolitis and asthma diagnostic management guidelines [10,11].

Through a subgroup analysis, we repeated the above analysis by excluding infants who had significant medical complications before postnatal discharge. The criteria for exclusion from this analysis were admission to Neonatal Intensive Care Unit (NICU), and/or receipt of ventilation or surfactant listed on the birth certificate or in CHARS records (described in Appendix 1). The Washington State Institutional Review Board determined this analysis exempt from human subjects approval. The analysis was conducted using Stata 13.1 (Statacorp, College Station, TX).

Results

Subjects

We identified 4267 electively induced early-term and 29 097 electively induced full- or late-term births for inclusion in this study. Maternal, pregnancy, and delivery characteristics, including age and race/ethnicity, were similar between infants born early-term and those born full- or late-term (Table 1). Mothers of early-term infants were observed to have slightly higher mean parity than mothers of full- or late-term infants (≥2 births: 40.2% versus 29.0%). Infants born full- or late-term were on average 295 g heavier than early-term infants and were more likely to be delivered via cesarean section (11.0% versus 6.8%). All variables included in our analysis had a low percentage of missing data with no discernible pattern.

Among children born via electively induced early-term delivery, there were a higher percentage of children admitted to the hospital before age five for a lower respiratory tract disorder than among children born full- or late-term (Table 2). There was a statistically significant decrease in the percentage of children admitted with lower respiratory tract conditions with increasing gestational age from 6.3% among those born at 37 weeks to 2.8% among those born at 41 weeks (Figure 1, trend test \( p < 0.0001 \)). The data also provide strong evidence that the percentage of children admitted two or more times for any lower respiratory tract condition decreased with increasing gestational age (\( p < 0.0001 \)).

Children born via electively induced early-term delivery had a significantly increased odds of being hospitalized before age five for any lower respiratory tract disease compared to those born via induced full- or late-term delivery (OR: 1.33, 95% CI: 1.14–1.56). This result persisted after adjustment for potential confounders (aOR: 1.31, 95% 1.11–1.55). Of the individual diagnoses comprising the primary outcome, only the odds of hospitalization for bronchiolitis was significantly increased for children born via elective early-term induction (aOR: 1.40, 95% CI: 1.12–1.75). The odds ratios for the less frequently diagnosed respiratory outcomes of asthma (aOR: 1.39, 95% CI: 0.93–2.08) and pneumonia (aOR: 1.27, 95% CI: 0.99–1.64) were increased to a similar degree, though were not statistically significant. Bronchitis diagnoses were too rare in the population to calculate a meaningful estimate of association, with only two cases of bronchitis in the early-term group. These adjusted estimates were not substantially different from the unadjusted estimates (Table 2).

When we repeated our analyses after excluding infants admitted to NICU and/or received ventilation or surfactant (4.92% early-term infants and 4.48% full- or late-term infants), we found almost no change in the magnitude of the association. In this subgroup, early-term delivery continued to increase the odds of hospitalization for lower respiratory tract disease compared to full- or late-term delivery (aOR: 1.32, 95% CI: 1.11–1.57, \( p = 0.001 \)).

Discussion

We found children born via electively induced early-term delivery were at increased risk of lower respiratory disorder hospitalizations before age five compared to children born via
electively induced full- or late-term delivery. When restricting the analyses to those children without admission to NICU, or ventilation or surfactant administration, the increased risk of hospitalization persisted. This subgroup analysis implies that the observed increased odds of hospitalization for lower respiratory tract disorders are unlikely to be mediated by neonatal complications. It is possible that subclinical effects of early-term delivery predispose infants to lower respiratory disorders during childhood.

In our study population, we identified a borderline, but non-significant, 39% increase in risk of asthma hospitalization, which is consistent with the 20% increased risk reported in a retrospective cohort study in Finland in 2014. Studies from both Australia and the United Kingdom have demonstrated a gradient of decreasing risk of hospital admission for asthma with increasing gestational age through 40 weeks [12,13]. Given that children born early-term have a slightly older gestational age and increased pulmonary maturity than those born late-preterm, our smaller estimate is expected. Currently, there is little research addressing the burden of bronchiolitis and pneumonia hospitalizations in children born early-term. However, as with asthma, we expected an association to be slightly lower than those identified in children born late-preterm. When comparing children born late-preterm to those born full-term, Bérard et al. found hazard ratios of 1.64 (95% CI: 1.13–2.39) for bronchiolitis diagnosis and 1.17 (95% CI: 1.05–1.30) for pneumonia diagnoses [4]. Our findings of a significant 40% increase in odds of bronchiolitis hospitalization and borderline significant 27% increase in odds of pneumonia hospitalization align with Bérard et al.’s findings. Further studies are warranted to assess the association between induced early-term delivery and pneumonia and asthma, given the borderline significant associations identified in our cohort.

### Table 1. Maternal, pregnancy, and infant characteristics.

|                      | Early-term (37–38 weeks) n = 4267 | Full- and late-term (39–41 weeks) n = 29 097 | Total (37–41 weeks) N = 33 364 |
|----------------------|----------------------------------|---------------------------------------------|--------------------------------|
| Maternal demographics|                                  |                                             |                                |
| Maternal age, mean (SD), years | 28.1 (5.56) | 27.4 (5.74) | 27.5 (5.72) |
| Missing, no. (%)     | 0 (0)                            | 0 (0)                                       | 0 (0)                           |
| Race, no. (%)        |                                  |                                             |                                |
| White                | 3539 (83)                        | 24 028 (83)                                 | 27 567 (83)                     |
| Black                | 97 (2.3)                         | 721 (2.5)                                   | 818 (2.5)                       |
| Hispanic             | 286 (6.7)                        | 2190 (7.5)                                  | 2476 (7.4)                      |
| Native American      | 71 (1.7)                         | 407 (1.4)                                   | 478 (1.4)                       |
| Asian                | 202 (4.7)                        | 1193 (4.1)                                  | 1395 (4.2)                      |
| Other                | 37 (0.87)                        | 257 (0.88)                                  | 294 (0.88)                      |
| Missing              | 35 (0.82)                        | 301 (1.0)                                   | 336 (1.0)                       |
| Type of insurance, no. (%) |                                  |                                             |                                |
| Public/charity       | 1315 (31)                        | 10 156 (35)                                 | 11 471 (34)                     |
| Private              | 2652 (62)                        | 17 290 (59)                                 | 19 942 (60)                     |
| Missing              | 300 (7.0)                        | 1651 (5.7)                                  | 1951 (5.9)                      |
| Pregnancy characteristics|                                  |                                             |                                |
| Smoked during pregnancy, no. (%) | 466 (11)                  | 2994 (10)                                   | 3460 (10)                       |
| Parity, mean (SD)    | 1.15 (0.79)                      | 0.90 (0.82)                                 | 0.93 (0.82)                     |
| 0, no. (%)           | 1054 (23)                        | 11 283 (39)                                 | 12 337 (37)                     |
| 1, no. (%)           | 1491 (35)                        | 9292 (32)                                   | 10 783 (32)                     |
| 2+, no. (%)          | 1714 (40)                        | 8422 (29)                                   | 10 136 (30)                     |
| Missing, no. (%)     | 8 (0.19)                         | 100 (0.34)                                  | 108 (0.32)                      |
| Delivery type, no. (%)|                                  |                                             |                                |
| Vaginal              | 3975 (93)                        | 25 882 (89)                                 | 29 857 (89)                     |
| C-section            | 292 (6.8)                        | 3215 (11)                                   | 3507 (11)                       |
| Missing              | 0 (0)                            | 0 (0)                                       | 0 (0)                           |
| Infant characteristics|                                  |                                             |                                |
| Birth weight, mean (SD), g | 3353 (430)                  | 3648 (421)                                  | 3611 (433)                      |
| Missing, no. (%)     | 0 (0)                            | 0 (0)                                       | 0 (0)                           |

### Table 2. Crude and adjusted odds ratios for lower respiratory tract disorder hospitalizations before age five for comparing children born via induced early-term delivery to full- or late-term delivery.

| Outcome          | Exposed cases (%) | Unexposed cases (%) | OR (95% CI) | aOR (95% CI) |
|------------------|-------------------|---------------------|-------------|--------------|
| Any respiratory  | 192 (4.50)        | 991 (3.41)          | 1.33 (1.14–1.56) | 1.31 (1.11–1.55) |
| Asthma           | 30 (0.70)         | 152 (0.52)          | 1.35 (0.91–1.99) | 1.39 (0.93–2.08) |
| Pneumonia        | 80 (1.87)         | 418 (1.44)          | 1.31 (1.03–1.67) | 1.27 (0.99–1.64) |
| Bronchiolitis    | 103 (2.41)        | 501 (1.72)          | 1.41 (1.14–1.75) | 1.40 (1.12–1.75) |
| Bronchitis       | 2 (0.05)          | 14 (0.05)           | 0.97 (0.22–4.28) | 0.66 (0.09–5.18) |
| Any respiratory  (for subgroup)* | 1.34 (1.14–1.58) | 1.32 (1.11–1.57) |

*Excluding infants who were ventilated, received surfactant, or were admitted to NICU (excluded n = 1652).
Our findings are consistent with biological theory. There are two hypothesized pathways that may link gestational age and childhood respiratory outcomes. The first is a direct pathway, whereby immature organ systems are vulnerable to exposures that produce long-lasting, if not permanent, dysfunction. While most neonates achieve independently viable pulmonary maturity by 35 weeks, early-term infants demonstrate a range of pulmonary maturity on amniotic fetal lung maturity (FLM) test. Furthermore, infants born early-term with a normal amniotic FLM score are at an increased risk of adverse neonatal outcomes [14,15]. This highlights that assessing surfactant production may not provide a comprehensive review of pulmonary or other organ system function [16]. Therefore, it is plausible that despite the adequate surfactant production expected by 37 weeks, pulmonary development may still be adversely influenced by early-term delivery. Our findings of decreasing childhood respiratory admissions with advancing term gestational age, including a decrease in multiple childhood respiratory admissions, further support the hypothesis that early-term delivery may impact long-term pulmonary function.

The second proposed pathway is mediated by perinatal interventions in response to perinatal morbidity. Infants born early-term have an increased risk of perinatal morbidity, such as hypoglycemia, apnea, and suspected sepsis, necessitating treatment with interventions, such as ventilation [3,6,17]. While these interventions are life-saving, they are associated with respiratory complications lasting into childhood [18]. Our subgroup analysis attempted to examine these pathways by excluding those children who had received ventilation and/or surfactant, and/or had been admitted to NICU. The number of infants excluded in our subgroup analysis due to requiring perinatal intervention was comparable to studies in the similar populations (<5%), and did not alter our results from the full data set [19].

Our analyses had several strengths. We attempted to minimize the misclassification of gestational age by including only children with a concordant gestational age by best clinical estimate and by last menstrual period within one week. Our cause-specific analyses restricted asthma diagnoses to those made in children older than 2 years and bronchiolitis diagnoses to those made in children younger than 2 years as these disorders are age-dependent. Finally, we excluded early-term deliveries that were clinically indicated. This exclusion minimized confounding by indication for early-term delivery.

The primary limitation of this study relates to the use of hospital discharge data. The majority of children with respiratory problems likely never experience symptoms severe enough to necessitate hospitalization. As such, our results are specific to lower respiratory tract disorder hospitalizations, rather than overall incidence of these diagnoses before age five. However, we view hospital admission as an important marker of severe disease rather than the incidence in the entire population. A second limitation is that we were unable to accurately identify those women laboring versus non-laboring at the time of cesarean. Therefore, we limited our cohort to inductions of labor. We did, however, include cesarean deliveries where an induction was followed by a cesarean section. Furthermore, we were unable to measure any demographic characteristics that may influence seeking care for childhood respiratory disorders. Finally, the hospitalizations of children in our cohort who were born in Washington State, but moved out of state during childhood, were not captured in CHARS records.

Our concern about misclassification between the ICD-9 codes for asthma, pneumonia, bronchiolitis, and bronchitis led us to combine these diagnoses into a single measure. However, misclassification between these conditions and non-respiratory disorders is unlikely. We also hypothesized that these four conditions may share a similar pathway between exposure and outcome. Thus, a combined lower respiratory disease measure is a more meaningful outcome than any single lower respiratory ICD-9 code.

In our population-based study, elective early-term induction was associated with childhood hospitalization for lower respiratory tract disorders before age five, even when excluding children with perinatal complications. These
findings add to the research on the risk of poor long-term outcomes among children born elective early-term compared to those born full- or late-term.

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**Declaration of interest**

All authors confirm that they have no declaration of interests to report.

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**Appendix 1**

Table A1. Study variable definitions.

| Variable                        | Birth certificate variables | ICD-9 procedure codes | ICD-9 diagnosis codes |
|---------------------------------|-----------------------------|-----------------------|-----------------------|
| Maternal and delivery characteristics |                             |                       |                       |
| Induction of Labor              |                             |                       |                       |
| Gestational Age                 | Estimated gestational age, Gestational length (days) | 73.01, 73.1, 73.4, 73.99*, 96.49* | 659.0, 659.1 |
| Mode of delivery                |                             |                       |                       |
| Vaginal                         | Vaginal delivery            | –                     | –                     |
| Cesarean                        | Cesarean section            | 74.0                  | –                     |
| Smoking                         | Smoked                      | –                     | –                     |
| Insurance type†                 |                             |                       |                       |
| Public/charity                  | Medicare, Medicaid, Other sponsor, Charity | –                     | –                     |
| Private                         | HMO, Commercial insurance, L & I, Self-Pay | –                     | –                     |
| Race                            | Mother’s race               |                       |                       |
| Parity                          | Number of previous live births | –                     | –                     |
| Birth weight                    | Birth weight                |                       |                       |
| Medical indications for delivery|                             |                       |                       |
| HIV                             | –                           | –                     | 0.42, V08            |
| Placenta previa                 | –                           | –                     | 641.0, 641.1, 603.5   |
| Vasa previa                     | –                           | –                     | 641.2, 656.0          |
| Abruptio                        | –                           | –                     | 641.3, 641.8, 641.9, 649.31, 649.32 |

(continued)
| Variable                        | Birth certificate variables | ICD-9 procedure codes | ICD-9 diagnosis codes                  |
|--------------------------------|-----------------------------|-----------------------|----------------------------------------|
| Hypertension                   |                             |                        | 642.0, 642.1, 642.2, 642.31,           |
|                                |                             |                       | 642.32, 642.41, 642.42,               |
|                                |                             |                       | 642.51, 642.52, 642.61,               |
|                                |                             |                       | 642.62, 642.7, 642.91, 642.92         |
| Renal disease                  |                             | 646.21, 646.22        |                                        |
| Liver disease                  |                             | 646.71                |                                        |
| Diabetes & glucose intolerance| Diabetes                    | 648.0, 648.8          |                                        |
| Cardiac disease                |                             | 648.5, 648.61, 648.62|                                        |
| Unstable lie                   |                             | 652.0                 |                                        |
| Aneuploidy, congenital anomaly | Down syndrome, other chromosomal anomaly, spinal bifida, heart malformations, omphalocele, infant gastroschisis, limb reduction defect, cleft lip, cleft palate, any malformation, infant hypospadia | 655.0, 655.1, 655.3, 655.4, 655.5, 655.6, 655.8 |
|                               |                             | 657.0                 |                                        |
| Polyhydramnios                 |                             | 658.0                 |                                        |
| Oligohydramnios                |                             | 656.1, 656.2          |                                        |
| Rh disease                     | Fetal distress              | 656.3, 659.7          |                                        |
| Small for gestational age      |                             | 656.5                 |                                        |
| PPROM, PROM                    |                             | 658.1, 658.2          |                                        |
| Intrauterine infection         | Chorioamnionitis            | 658.4                 |                                        |
| Poor obstetric history         | Prior poor pregnancy outcome| V23.5                 |                                        |
| Subgroup exclusion criteria    | Assisted ventilation required| 96.7, 96.71, 96.72, 00.12, 34.04 |                                        |
|                                | immediately after delivery,  |                       |                                        |
|                                | assisted ventilation required| >6 h                  |                                        |
| Surfactant                     | Surfactant replacement therapy|                       |                                        |
| NICU admission                 | Neonatal ICU                |                       |                                        |

*Indicates codes utilized in addition to published Joint Commission codes for medical indications for early-term delivery.
†Payer ID from Washington State Comprehensive Hospital Abstract Reporting System (CHARS).