Original Article
Late preterm birth: an iatrogenic epidemic

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Abstract: Objective: We evaluated whether the recorded indications for late preterm delivery were supported by generally accepted medical indications in a cohort of late preterm birth (LPTB). In addition, we compared neonatal outcomes in cases of LPTB with and without generally accepted medical indications. Methods: We conducted a retrospective cohort study of LPTB from 2007-2009 in two tertiary care centers and two community hospitals in Salt Lake City, UT. Subjects delivered a live born infant between 34-36 6/7 weeks' gestation. Data were abstracted from maternal and neonatal medical records. An instrument created prior to data collection explicitly defined criteria for generally accepted medical indications for iatrogenic LPTB. Major neonatal morbidity was defined as a composite outcome of death in the first 120 days of life, intraventricular hemorrhage, necrotizing enterocolitis, and need for mechanical ventilation. Results: 244 cases of LPTB were analyzed. 18.9% of LPTB cases (46/244) did not meet criteria for a generally accepted medical indication for late preterm delivery. The recorded diagnoses ‘placenta previa’, ‘oligohydramnios’, ‘preeclampsia’, ‘maternal disease’, and ‘placental abruption’ were most likely to fail to meet criteria for generally accepted indication after review of primary medical records. LPTB without generally accepted medical indication was associated with an increased risk of composite major neonatal morbidity (19.1% vs. 7.9%, P = 0.03). Need for neonatal ventilator support was independently associated with LPTB without generally accepted medical indication (19.1% vs. 6.9%, P = 0.02). Conclusion: Almost one fifth of LPTB, and its neonatal sequelae, may be avoidable.

Keywords: Iatrogenic preterm birth, late preterm birth, neonatal morbidity, prematurity

Introduction
Late preterm birth (LPTB), defined as delivery between 34 0/7 and 36 6/7 weeks’ gestation, remains a significant and common cause of neonatal morbidity and mortality [1, 2]. In 2011, the overall rate of preterm birth in the United States declined for the fifth straight year to 11.73%, a decrease of 8% since 2006 [3]. Modest declines in the rate of LPTB have contributed to this trend. Since 2006, LPTBs have declined 11% to a rate of 8.28% [3]. Recent efforts to reduce non-medically indicated late preterm deliveries might have contributed to this rate reduction. Despite recent trends, the overall preterm birth rate remains higher than during the 1980s and 1990s. Importantly, LPTB continues to constitute more than 70% of all preterm births.

Over the past forty years, most research and clinical efforts directed at preterm birth were aimed at reducing the rate of birth at less than 34 weeks gestation. These efforts were based on the fact that by 34 weeks gestation, perinatal outcomes are generally good with a mortality rate of less than one percent [4, 5]. However, infant mortality rates remain substantially higher in LPTBs compared to term births [5-11]. In addition to mortality, late preterm infants have higher rates of morbidity than those born at term [10-12]. LPTB results in higher rates of respiratory morbidities [10-12], infections [11], intraventricular hemorrhage [11], feeding difficulties [13, 14], hyperbilirubinemia [15], hypoglycemia and hypothermia [16], compared to term birth. Late preterm infants also may have an increased risk for long term medical complications including cerebral palsy, neurodevelopmental delay, behavioral problems, communication impairments, and an increased risk of poor reading and math skills compared to term infants [11, 17-21]. Late preterm infants also
### Table 1. Definitions of Generally Accepted Indications for Iatrogenic Preterm Delivery*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Criteria</th>
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</table>
| **1. Preeclampsia/Eclampsia** | a. Blood pressure of 160 mmHg systolic or higher or 110 mmHg diastolic or higher on two occasions at least six hours apart while the patient is on bed rest  
b. Proteinuria of 5 g or higher in a 24-hour urine specimen or 3+ or greater on two random urine samples collected at least 4 hours apart  
c. Oliguria of less than 500 mL in 24 hours  
d. Neurologic changes or visual disturbances  
e. Pulmonary edema or cyanosis  
f. Epigastric or right upper-quadrant abdominal pain  
g. Impaired liver function  
h. Thrombocytopenia  
i. Fetal growth restriction |
| **2. Preterm Premature Rupture of Membranes (PPROM)** | a plus b  
a. Confirmed PROM with visualization of fluid passing from the cervical canal, positive nitrazine test, or positive ferning of fluid taken from the posterior fornix  
b. Gestational age greater than 34 weeks gestation |
| **3. Preterm Labor** | a and b  
a. Regular contractions of the uterus  
b. Documented change in cervical dilation or effacement |
| **4. Abnormal Antepartum Fetal Surveillance** | One or more of the following:  
a. Positive contraction stress test  
b. Biophysical profile of 4 or less  
c. Biophysical profile of 6 that persists for 24 hours  
d. Umbilical artery Doppler velocimetry with reverse diastolic flow |
| **5. Oligohydramnios** | One or more of the following:  
a. Amniotic fluid index less than 2 cm  
b. Deepest vertical pocket of amniotic fluid less than 1 cm  
c. Amniotic fluid index less than 5 cm with abnormal antepartum fetal surveillance (non-reactive non-stress test or abnormal Doppler velocimetry with absent or reversed end diastolic velocity), preeclampsia, or small for gestational age fetus (estimated fetal weight less than 10% for gestational age) |
| **6. Small for Gestational Age Fetus** | a or b, plus c, d, e, f, or g  
a. Estimated fetal weight less than 5th percentile for gestational age  
b. Abdominal circumference less than 5th percentile for gestational age  
c. Non-reactive non stress test  
d. Biophysical profile of 6 or less  
e. No significant interval fetal growth in three weeks  
f. Amniotic fluid index of less than 5 cm or deepest vertical pocket less than 2 cm |
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g. Umbilical artery Doppler velocimetry with absent or reversed end diastolic velocity

7. Placenta Previa
   a. plus b, c, d, or e
      a. Placenta previa documented by ultrasound
      b. Acute vaginal bleeding
      c. Regular uterine contractions indicative of labor
      d. Abnormal fetal heart rate tracing
      e. Fetal pulmonary maturity

8. Placental Abruption
   a or b
      a. Placental abruption documented by ultrasound
      b. Acute vaginal bleeding with no placenta previa

9. Prior Stillbirth

10. Elective Delivery [37]
    a. Fetal pulmonary maturity

11. Maternal Medical Disease (e.g., diabetes, congenital heart disease, cancer)
    One or more of the following:
       a. Fetal pulmonary maturity
       b. Recommendations by medicine subspecialist (including maternal-fetal medicine physician or other disease-specific subspecialist) that iatrogenic delivery is indicated for the mother

12. Fetal Malformations, Genetic Conditions, or Abnormalities
    One or more of the following:
       a. Fetal pulmonary maturity
       b. Lethal abnormality
       c. Desire to achieve vaginal birth in case of grave prognosis (e.g., macrocephaly with hydrocephalus)
       d. Desire to improve neonatal outcome with postnatal intervention (e.g., hydrops)

13. Multiple Gestation
    One or more of the following:
       a. Twin-twin transfusion stage II, III, or IV
       b. Mono-amniotic or mono-chorionic twin gestation
       c. Other indication for delivery as above

*The criteria were based on current ACOG Committee Opinions, Guidelines, and Technical Educational Bulletins, as well as consensus expert opinion.
have increased length of hospital stays, rates of readmission (after discharge) and higher medical costs (persisting through the first year of life) than term births [22, 23].

We hypothesized that, in a proportion of cases, LPTB occurs without generally accepted medical indication. These cases are of particular concern, because they should be preventable. We also hypothesized that LPTB without identifiable accepted medical indication is associated with increased neonatal morbidity when compared with indicated LPTB.

Materials and methods

This retrospective cohort study of LPTB was conducted in four Salt Lake City hospitals, including two tertiary care centers and two community hospitals. Women were eligible for inclusion in the study if they delivered a live born infant 34 0/7 to 36 6/7 weeks’ gestation between 2007 and 2009 at a participating hospital. Consecutive cases were identified through screening labor and delivery logs and data were abstracted from maternal and neonatal medical records. Institutional Review Board approval was obtained from all four participating hospitals. The hospitals were chosen to include a mixture of tertiary care centers and community hospitals.

Two hundred fifty LPTBs were studied. However, complete medical records were not available for six patients. Thus, a total of 244 LPTBs had detailed abstraction of maternal and neonatal medical records, including 108 delivered at the University of Utah Health Sciences Center, 79 at the Latter Day Saints Hospital, 27 at Alta View Hospital, and 30 at Cottonwood Hospital. The University of Utah and Latter Day Saints Hospitals are tertiary care centers (N = 187), and Alta View and Cottonwood are community hospitals (N = 57). The latter two hospitals transported infants delivered at < 36 weeks gestation. Thus, they had considerably fewer LPTBs than the other hospitals. Maternal and neonatal medical records were abstracted by trained research personnel. Available records included prenatal records, delivery records, and ultrasound data.

We determined whether the recorded indication for delivery was well supported by generally accepted medical indications in this cohort. An instrument created prior to data collection was used to explicitly define criteria for generally accepted medical indications for late preterm delivery. The criteria were based on current ACOG Committee Opinions, Guidelines, and Technical Educational Bulletins, as well as consensus expert opinion. The quality of evidence supporting the recorded indication for late preterm delivery was assessed using this instrument, which is shown in Table 1.

Gestational age was defined using the last menstrual period. If the last menstrual period was unsure, or if the woman’s menstrual cycles were irregular in interval, the measurements obtained at the mother’s first ultrasound examination was used to determine gestational age. If the last menstrual period was reliable, the gestational age based on last menstrual period was compared with the first ultrasound. If they did not agree, ultrasound dating was used.

Descriptive statistics were used to assess maternal demographics and pregnancy characteristics. The proportion of LPTBs associated with generally accepted medical indications,

Table 2. Demographic and Pregnancy Characteristics of Late Preterm Births*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (% )</th>
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<tbody>
<tr>
<td>Race/ethnicity, n (%)</td>
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<td></td>
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</tr>
<tr>
<td>Caucasian, non-Hispanic</td>
<td>164 (67.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American, non-Hispanic</td>
<td>3 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>62 (25.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age, yrs, mean (range)</td>
<td>27.9 (15-42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of pregnancies, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>79 (32.4)</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>60 (24.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>105 (43.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age at delivery, mean (range)</td>
<td>35.8 (34 0/7-36 6/7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple birth pregnancy, n (%)</td>
<td>11 (4.5)</td>
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</tbody>
</table>

*244 women were included in the analysis.
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Table 3. Proportion of Late Preterm Births Without Generally Accepted Indication, Stratified by Recorded Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>n/N*</th>
<th>% Deliveries Without Medical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta previa</td>
<td>3/5</td>
<td>60.0</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>8/15</td>
<td>53.3</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>18/36</td>
<td>50.0</td>
</tr>
<tr>
<td>Maternal disease</td>
<td>5/10</td>
<td>50.0</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>3/6</td>
<td>50.0</td>
</tr>
<tr>
<td>Fetal abnormality</td>
<td>6/16</td>
<td>37.5</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>4/11</td>
<td>36.4</td>
</tr>
<tr>
<td>Abnormal fetal surveillance</td>
<td>3/14</td>
<td>21.4</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>2/11</td>
<td>18.1</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>15/113</td>
<td>13.3</td>
</tr>
<tr>
<td>At least one condition**</td>
<td>46/244</td>
<td>18.9</td>
</tr>
</tbody>
</table>

*n = number of women who met criteria for accepted medical indication on review of primary medical records; N = total number of women with this indication listed as the reason for late preterm delivery. **Based on 244 women studied; indications were not mutually exclusive and some women had > 1 documented indication for delivery.

We considered variables that could potentially be associated with late preterm delivery without generally accepted indication (Table 4). None of the characteristics assessed were significantly associated with an increased risk for having a LPTB without a generally accepted indication. There were trends towards an increased risk for unindicated late preterm delivery in non-Hispanic Caucasians, mothers > 35 years of age, nulliparas, grand multiparas, private hospitals, pregnancies conceived with assisted reproductive technology (ART), later gestational ages, and pregnancies complicated by hypertension or diabetes.

Discussion

This retrospective cohort study suggests that almost one fifth of LPTB, and its neonatal sequelae, is potentially avoidable. An even higher proportion of cases did not have a generally accepted medical indication if the recorded indication of ‘preterm labor’ is excluded. Overall, almost 19% of LPTB cases (46/244) did not meet criteria for a generally accepted medical indication (Table 3). If the recorded indication of ‘preterm labor’ is excluded, 23.7% (31/131) had no generally accepted medical indication after review of the primary data. The recorded diagnoses ‘placenta previa’, ‘oligohydramnios’, ‘preeclampsia’, ‘maternal disease’, and ‘placental abruption’ had the highest percentage of cases without a generally accepted indication. (Table 3). LPTB without identifiable accepted medical indication was associated with an increased risk of composite major neonatal morbidity consisting of death in the first 120 days of life, intraventricular hemorrhage, necrotizing enterocolitis, and mechanical ventilation (19.1% versus 7.9%; p = 0.03). The composite was driven by the need for mechanical ventilation, which was associated with late preterm delivery without generally accepted medical indication (19.1% versus 6.9%; p = 0.02). There was no difference in rates of respiratory distress syndrome, hypoglycemia or jaundice between groups (data not shown).
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Reddy and colleagues assessed 292,627 deliveries between 34 and 36 weeks gestation in 2001 using National Center for Health Statistics (NCHS) 2001 Birth Cohort Linked Birth/Death files [24]. Based on vital statistics data, 67,909 (23.2%) of these births had no recorded indication. Gyamfi and colleagues reported that 56.7% of iatrogenic LPTBs occurred without “evidence based” indications in an overall cohort of 2,696 cases of LPTB in two health care systems [25]. In our cohort, preeclampsia and oligohydramnios were the most common diagnoses associated with iatrogenic LPTB that did not meet generally accepted criteria for delivery. Similarly, mild preeclampsia contributed over half of the “potentially avoidable” cases of LPTB in the Houston cohort [26]. Small for gestational age fetuses and maternal medical diseases in the setting of normal fetal testing also contributed to “avoidable” LPTB in the Houston cohort, as well as in the current study.

Another important cause of “non-indicated” or “potentially avoidable” late preterm delivery is the practice of augmenting prodromal labor in women with preterm uterine contractions. For example, a patient at 36 weeks gestation may have uterine activity without cervical change. Such patients may receive augmentation with oxytocin leading to a potentially unnecessary LPTB. Moreover, it will be recorded as spontaneous preterm labor in the medical records, making it difficult to ascertain without review of the primary data. In our cohort, in which primary records were reviewed, over 13% of cases of LPTB due to the recorded indication of ‘preterm labor’ were cases of augmented prodromal labor without preceding cervical change. We believe this an under-appreciated cause of unnecessary LPTB and an important target for LPTB prevention strategies.

We considered variables that could potentially be associated with late preterm delivery without generally accepted medical indication, but none of the characteristics assessed were statistically associated with an increased risk for having a LPTB without a generally accepted indication. There were interesting trends towards an increased risk for non-indicated late preterm delivery in non-Hispanic Caucasians, mothers > 35 years of age, nulliparas, grand multiparas, private hospitals, pregnancies conceived with ART, later gestational ages, and pregnancies complicated by hypertension or diabetes. However, the sample size was inade-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, non-Hispanic</td>
<td>Reference</td>
<td>0.22</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.60 (0.27, 1.33)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.25 (0.03, 1.98)</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35</td>
<td>Reference</td>
<td>0.48</td>
</tr>
<tr>
<td>≥ 35</td>
<td>1.44 (0.52, 4.01)</td>
<td></td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>1</td>
<td>Reference</td>
<td>0.48</td>
</tr>
<tr>
<td>2</td>
<td>0.71 (0.28, 1.83)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>1.39 (0.67, 2.91)</td>
<td></td>
</tr>
<tr>
<td>Teaching hospital</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Private hospital</td>
<td>1.31 (0.68, 2.52)</td>
<td></td>
</tr>
<tr>
<td>Assisted reproductive technology</td>
<td>2.18 (0.39, 12.29)</td>
<td>0.38</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>&lt; 35 weeks</td>
<td>Reference</td>
<td>0.29</td>
</tr>
<tr>
<td>35 0/7-35 6/7 weeks</td>
<td>2.06 (0.69, 6.17)</td>
<td></td>
</tr>
<tr>
<td>36 0/7-37 weeks</td>
<td>2.28 (0.82, 6.33)</td>
<td></td>
</tr>
<tr>
<td>Maternal disorders</td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.20 (0.39, 12.39)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.00 (0.59, 6.79)</td>
<td>0.27</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1.08 (0.12, 9.90)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Odds ratio, 95% confidence interval. Results are univariate statistics.
quate to evaluate these associations or to perform a meaningful multivariable logistic regression model. Older maternal age, non-Hispanic Caucasian race/ethnicity, multiparity, ≥ 13 years of education and prior large for gestational age infant were associated with having a lack of a recorded indication for LPTB in the 2001 US Birth Cohort [24]. Non-faculty physician status, later gestational age (37 weeks versus 34 weeks), and prior cesarean delivery were risk factors for potentially avoidable LPTB in the Houston study [26]. Twin pregnancy and private insurance status have also been associated with non-evidence based LPTB [25]. The reasons for non-evidence based LPTB are not entirely clear, and likely involve a combination of physician and patient driven factors [27]. It stands to reason that physicians and patients may be more anxious in certain scenarios (e.g. older, nulliparous women conceived with ART), possibly leading to a lower threshold for elective late preterm delivery.

In addition to inadequate sample size to assess risk factors for LPTB without generally accepted medical indication, our study has other weaknesses. The study was not population based, and not all cases of LPTB were included from each hospital. Cases were ascertained consecutively making systematic bias unlikely. Nonetheless, the inclusion criteria and retrospective design were potential sources of bias. In addition, we did not have access to all medical records in all cases. Outpatient data not recorded in the prenatal record and encounters at outside facilities were not available for detailed review. Therefore, while record review was rigorous, it is possible that pertinent data, such as additional blood pressures indicative of preeclampsia or ultrasound results indicating oligohydramnios, were not available. This may result in over estimation of the rate of late preterm delivery without generally accepted medical indication. The presence of several risk factors in combination (e.g. mild preeclampsia, oligohydramnios, and advanced maternal age) may have led to a rea-sonable clinical decision for iatrogenic late preterm delivery. We were unable to account for this type of decision making in this analysis. Finally, two-thirds of our patients were Caucasian and we had very few African Americans. This may limit generalizability of our results. However, few other studies have focused on Caucasian, who have been shown to have an increased risk for LPTB [28].

In February 2011, the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Society for Maternal Fetal Medicine held a workshop on the “timing of Indicated Late Preterm and Early Term Births.” Among other goals, the workshop aimed to determine optimal delivery timing for a variety of maternal, fetal, and obstetrical complications using available data and expert opinion. The resulting document was published in August 2011 [29]. Recommendations regarding medical indications for late-preterm delivery were also published in a 2013 ACOG Committee Opinion [30]. These guidelines were not available at the time this study was conducted and some discrepancies exist between our definitions of generally accepted indications for iatrogenic preterm delivery and the definitions published as a result of the workshop. Contemporary cohorts of late preterm birth need to be evaluated with these newer guidelines in mind.

Our study also had several strengths. A significant problem with available LPTB data is a lack of detailed obstetric information. Most studies are derived from large vital statistics databases [6, 7]. They include large numbers of patients but relatively superficial information that may be incorrect. Several investigators have demonstrated considerable discrepancies in data derived from birth certificates compared to chart abstraction [31, 32]. Even if the diagnosis is corrected captured, it may not be accurate based on medical criteria. For example, a case coded as preeclampsia may not actually meet criteria for the disease. In order to truly determine the validity of indications for late preterm deliveries, a careful review of detailed medical data including blood pressures, laboratory values, ultrasounds, and fetal heart rate tracings is required. Our use of experienced obstetric research nurses to perform chart abstraction ensured accurate data collection.

Another problem with available studies is a tendency to include only data from tertiary care centers that serve as teaching hospitals [5]. The medical care in teaching hospitals may not accurately reflect general community practice. Residents in training are generally educated on the most up-to-date studies and recommendations for evidence based practice and many physicians review each case during the course of teaching rounds. Accordingly, it may be less
likely for preterm births without generally accepted medical indications to occur in a teaching hospital than in other settings. Also, tertiary care centers usually have a referral population that is skewed towards patients with greater acuity. Thus, the relative contribution of conditions such as preterm labor and preeclampsia to LPTB likely varies considerably between tertiary care and community hospitals. By including subjects from both tertiary care and community hospitals, our cohort better captures the overall rate of non-indicated LPTB in our community.

In summary, almost one fifth of LPTBs, and associated neonatal sequelae, were potentially avoidable in this retrospective cohort. Moreover, LPTB without identifiable generally accepted medical indication was associated with an increased risk of neonatal morbidity. These data underscore the importance of continued physician education regarding the risks of LPTB and the need to adhere to generally accepted medical indications for iatrogenic late preterm delivery. Quality improvement efforts should focus on reducing augmentation of pre-dramal preterm labor in patients without cervical change prior to 37 weeks’ gestation. The optimal mechanism of administrative and clinical oversight needs to be determined. Further research is needed to determine the optimal balance between prematurity and consequences of continuing at-risk pregnancies. Until then, these data provide further evidence that late preterm delivery should be avoided unless clear medical indication exists.

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Disclosure of conflict of interest

None.

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