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OBSTETRICS

# A multicenter prospective study of neonatal outcomes at less than 32 weeks associated with indications for maternal admission and delivery

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**BACKGROUND:** Counseling for patients with impending premature delivery traditionally has been based primarily on the projected gestational age at delivery. There are limited data regarding how the indications for the preterm birth affect the neonatal outcome and whether this issue should be taken into account in decisions regarding management and patient counseling.

**OBJECTIVE:** We performed a prospective study of pregnancies resulting in premature delivery at less than 32 weeks to determine the influence of both the indications for admission and their associated indications for delivery on neonatal mortality and complications of prematurity.

**STUDY DESIGN:** This is a multicenter, prospective study in 10 hospitals where all data from the neonatal intensive care unit routinely was imported to a deidentified data warehouse. Maternal data were collected prospectively at or near the time of delivery. Eligible subjects included singleton deliveries in these hospitals between 23 0/7 and 31 6/7 weeks. The primary hypothesis of the study was to determine whether there was a difference in the primary outcome, which was defined as neonatal composite morbidity, between those neonates delivered after admission for premature labor vs premature rupture of membranes, because these were expected to be the 2 most frequent diagnoses leading to premature birth. The sample size was calculated based on a 10% difference in outcomes for these 2 entities. We based this hypothesis on the knowledge that premature rupture of membranes has a greater incidence of intra-amniotic infection and inflammation than premature labor and that outcomes for premature neonates are worse when delivery is associated with intra-amniotic infection. Additional outcomes were analyzed for all other indications for admission and delivery. Composite morbidity was defined as $\geq$1 of the following: respiratory distress syndrome (oxygen requirement, clinical diagnosis, and consistent chest radiograph), bronchopulmonary dysplasia (requirement for oxygen support at 28 days of life), severe intraventricular hemorrhage (grades 3 or 4), periventricular leukomalacia, blood culture-proven sepsis present within 72 hours of birth, necrotizing enterocolitis, or neonatal death before discharge from the hospital. A secondary composite of serious neonatal morbidity also was defined prospectively.

**RESULTS:** The study included 1089 mother/baby pairs. Composite morbidity between those with premature labor (77.2%) and premature rupture of membranes (73.2%) was not significantly different ($P = .29$). A few neonatal complications were associated with indications for admission and delivery, but on logistic regression adjusting for gestational age and other confounders, suspected intrauterine growth restriction was the only indication for admission or delivery associated with an increase in serious morbidity (odds ratio 4.5, [2.1 to 9.8], $P < .003$). Other factors not related to the indications for admission including cesarean delivery, and low 5-minute Apgar were associated with an increase in morbidity.

**CONCLUSION:** Studies of many single factors related to the indications for preterm delivery have been shown to be associated with adverse neonatal outcome. In this study evaluating all of the most frequent indications, however, we found only suspected intrauterine growth restriction as an indication for admission and delivery was found to be so. Thus, it seems that in almost all situations counseling patients can be based primarily on gestational age along with other factors including estimated fetal weight, sex, race, plurality, and completion of a course of antenatal corticosteroids.

**Key words:** neonatal outcomes, maternal admission and delivery, premature labor, premature rupture of membranes, intrauterine growth restriction

For the prematurely delivering neonate, both the obstetrician/perinatologist and the pediatrician/neonatologist must have the most accurate information possible regarding the likelihood of survival and the magnitude of risk of complications the preterm neonate will face. For the obstetrician, this knowledge affects the ability to counsel parents and provide prognostic information for the neonatal outcome, to make decisions regarding whether to deliver early, and to decide on the best route of delivery in the periviable period. For the pediatrician, this information affects decisions regarding whether to resuscitate, what diagnostic tests to order or perform, what treatments to administer, and whether to sustain or withdraw mechanical ventilation and other life support methods. These decisions traditionally have been based on the best estimate of gestational age at the anticipated or actual time of delivery. Extensive literature is available on the likelihood of outcome

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based on gestational age at delivery.[1-3] More recently, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development has advocated the use of other factors in addition to the estimated gestational age, including birth weight, the baby's sex, singleton birth, and completion of a course of antenatal corticosteroids.[4] Collectively, these data can be used to give best estimates of the likelihood of survival and morbidity in the neonatal period as well as the best information for patient counseling.

There have been limited data, however, regarding how the indication for the premature delivery affects the outcome of the neonate at each gestational age. There are 2 reasons this information might be of importance. The indication for admission for impending preterm delivery is known at the time counseling and management decisions are made. Also, there are numerous studies showing that many of the complications associated with the indications for delivery are known to adversely affect neonatal outcome. For example, abruptio placentae, a relatively common reason for preterm delivery, is associated more frequently with hypoxia and acidosis,[5-9] which are factors known to affect survival and likelihood of neonatal complications such as intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), and even necrotizing enterocolitis (NEC).[8-13] Preterm premature rupture of membranes (PPROM) is more likely to be associated with infection and inflammation and adverse neonatal outcome than preterm labor or maternal reasons for delivery.[14-19] Infection and inflammation are known to be associated with neonatal sepsis, periventricular leukomalacia (PVL), and other complications.[19-23] Growth-restricted neonates, especially when associated with evidence of potential acidosis and/or impending fetal death, which often is a reason for delivery, have a greater rate of mortality and the most newborn complications.[24]

The vast majority of these studies comparing outcomes for the various indications for delivery, however, are retrospective, with limited and often-unreliable information regarding the indications for delivery. In addition, attempting to compare the effect of one indication to the other between studies are unlikely to be valid because the populations studied usually differ. Furthermore, it often is difficult to accurately define both the indication for admission and the reason for delivery in retrospective studies, especially if databases or neonatal records are used. For example, PPROM may be the indication for admission to the hospital, but the actual indication for proceeding to delivery may be chorioamnionitis, fetal distress, or preterm labor (PTL). Finally, the perinatal complications associated with these various indications leading to premature delivery are most likely in the very preterm gestational ages.

For these reasons, we chose to perform a prospective observational study of obstetric admissions leading to preterm delivery of neonates <32 weeks and carefully identify both the indications for admission and for delivery with the objective of determining whether the indications for admission and delivery have an impact on neonatal outcome beyond gestational age alone.

## Materials and Methods

We chose as the primary hypothesis that there would be a difference in neonatal outcome between those who were admitted for PTL as opposed to PPROM. We based this hypothesis on the knowledge that PPROM has a greater incidence of intra-amniotic infection and inflammation than PTL[14-19] and outcomes for premature neonates are worse when delivery is associated with intra-amniotic infection.[19-23]

We performed a multicenter prospective study in the Pediatrix/Obstetrix Perinatal Collaborative Research Network. One of the important features of this network is its Neonatal Data Warehouse, which includes deidentified data from the neonatal intensive care units in which its doctors practice and the data are derived directly from the electronic medical record of the neonates in each unit on a real-time basis. This data set has been used by the National Institutes of Health,[25,26] the Food and Drug Administration,[27] the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development Pediatric Trials Network,[28,29] and others to define and evaluate national trends in neonatal intensive care unit diagnoses and therapies. Ten hospitals were included in this study, including only those which had both Obstetrix MFM practices and Pediatrix neonatology practices. Institutional review board approval for the study with waiver of consent was obtained at each hospital.

Maternal data were collected at or near the time of delivery or within a few days of maternal discharge by trained research coordinators. Indications for maternal admission and indications for delivery were identified from admission and delivery notes. Indications for admission and delivery were not predefined. The indications were based on the judgment of the clinician as being significant enough to warrant admission or delivery. Any question requiring clarification about the indication for maternal admission or for delivery was addressed by the research coordinators directly with the admitting or delivering clinician as applicable and/or the principle investigator at that institution. To quantify interobserver variability in the coding of the primary reasons for admission and delivery, a blinded audit of a random sampling of cases was conducted by 3 of the investigators (T.J.G., C.A.C., K.M.) after the first 100 case reports were completed. The audit showed excellent agreement of case reports with the auditors' conclusions (87% agreement) and agreement of the auditors with each other (91% agreement). Monthly conference calls were held to clarify the criteria for these data and to review equivocal cases.

Subjects eligible for this study included all patients with singleton stillborn or live newborns delivered at these hospitals with a gestational age at delivery of between 23 0/7 and 31 6/7 weeks. This gestational age was chosen based on the knowledge that the vast majority of mortality and morbidity associated with premature birth occurs

**TABLE 1**
**Admission characteristics**

| | PPROM (n = 310) | PTL (n = 263) | Preeclampsia (n = 288) | IUGR (n = 59) | Bleeding (n = 38) | Short cervix (n = 37) | *P* value |
|---|---|---|---|---|---|---|---|
| Gestational age, wk, mean ± SD | 27.1 ± 2.7 | 27.7 ± 2.6 | 28.3 ± 2.2 | 28.2 ± 2.3 | 26.7 ± 2.9 | 24.4 ± 2.3 | <.001 |
| Maternal age, y, mean ± SD | 29.7 ± 6.0 | 28.1 ± 6.0 | 29.9 ± 6.5 | 28.6 ± 5.6 | 28.9 ± 6.2 | 29.4 ± 5.6 | .0244 |
| Nulliparity, n (%) | 100/292 (34) | 108/255 (42) | 133/282 (47) | 22/59 (27) | 7/33 (21) | 17/35 (49) | .0053 |
| Prenatal care, n (%) | 290/298 (97) | 247/255 (97) | 273/284 (96) | 57/59 (97) | 34/36 (94) | 33/36 (92) | .4514[a] |
| Race/ethnicity, n (%) | 299 | 257 | 284 | 59 | 36 | 36 | .6140 |
| White | 163 (55) | 139 (54) | 142 (50) | 33 (56) | 21 (58) | 19 (53) | |
| Hispanic | 67 (22) | 51 (20) | 61 (21) | 9 (15) | 4 (11) | 5 (14) | |
| Black | 32 (11) | 25 (10) | 35 (12) | 6 (10) | 7 (19) | 8 (22) | |
| Asian | 11 (4) | 18 (7) | 13 (5) | 3 (5) | 3 (8) | 2 (5) | |
| Other | 26 (8) | 24 (9) | 33 (11) | 8 (14) | 1 (3) | 2 (5) | |

*P* value column is based on $\chi^2$ or the Fisher exact test ([a]) for categorical variables and Kruskal-Wallis test for continuous variables.

*P* value tests for statistical significance across all 6 groups are shown.

*IUGR*, intrauterine fetal growth restriction; *PPROM*, preterm prelabor rupture of membranes; *PTL*, preterm labor; *SD*, standard deviation.

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during this gestational age window.[2,3] Gestational age was based on an assessment of last menstrual period (LMP) and earliest reliable ultrasound examination dating. If the LMP is unknown or uncertain, ultrasound dating using standard criteria was used.[30] If the LMP and earliest ultrasound were not in agreement, then the dating was based on the earliest reliable ultrasound. Exclusions included patients with multiple gestations and live born babies never admitted to the neonatal intensive care unit.

The endpoint for the primary hypothesis was neonatal composite morbidity differences between patients admitted for PTL vs PPROM. Composite morbidity was defined as ≥1 of the following: RDS (oxygen requirement, clinical diagnosis, and consistent chest radiograph), bronchopulmonary dysplasia (BPD; requirement for oxygen support at 28 days of life), severe IVH (grades 3 or 4), PVL, blood culture-proven sepsis present within 72 hours of birth, NEC, or neonatal death before discharge from the hospital. Secondary outcomes included composite morbidity for all other indications for admission and delivery as well as mortality difference between all groups and individual morbidities including grades 3 or 4 IVH, PVL, RDS requiring need for oxygen for at least 24 hours and a consistent chest radiography, blood culture-proven sepsis, seizures, BPD, defined as need for continuous oxygen support beyond 28 days of life, and NEC. We also created a category of "serious morbidity" to compare neonatal outcomes, which included any one or more of the following: death, grade 3 or 4 IVH, ≥28 days on ventilator, blood culture-proven sepsis, PVL, and/or NEC > category II.[31] Beyond defining RDS, BPD, and sepsis as described previously, the data included were derived from the clinician's diagnosis in the medical record.

## Statistical analysis

Statistical analyses were performed as follows. Admission and delivery characteristics were tested for statistical significance across the reason for admission groups with the $\chi^2$ test or Fisher exact test for dichotomous or categorical variables, and the Kruskal-Wallis test for continuous variables. The null hypothesis for the primary outcome is that there is no difference in composite neonatal morbidity between neonates delivered after PTL and after PPROM. The percentage of neonates with the composite neonatal morbidity was calculated for neonates delivered after PTL and PPROM. Differences between the PTL and PPROM groups were tested for statistical significance with the $\chi^2$ test. Neonatal outcomes also were tested for statistical significance across the reason for admission and reason for delivery groups using the $\chi^2$ test or Fisher exact test for dichotomous or categorical variables and the Kruskal-Wallis test for continuous variables.

A stepwise logistic regression analysis of serious neonatal morbidity was completed. The model included as independent variables all reason for admission variables (using the PTL category as the reference) and prognostic factors for serious neonatal morbidity including all admission characteristic variables, gestational age at delivery, route of delivery, newborn sex, receipt of optimal antenatal corticosteroids, pH < 7.1, and Apgar < 5. A backwards procedure was used to select those variables associated most strongly with

**TABLE 2**
**Delivery characteristics**

| | PPROM (n = 310) | PTL (n = 263) | Preeclampsia (n = 288) | IUGR (n = 59) | Bleeding (n = 38) | Short cervix (n = 37) | *P* value |
|---|---|---|---|---|---|---|---|
| Gestational age, wk, mean ± SD | 28.5 ± 2.5 | 28.1 ± 2.5 | 28.9 ± 2.1 | 29.1 ± 2.2 | 27.4 ± 2.6 | 26.3 ± 2.6 | <.0001 |
| Interval from admission to delivery, wk, mean ± SD | 1.4 ± 1.6 | 0.4 ± 0.7 | 0.6 ± 0.7 | 0.9 ± 1.1 | 0.7 ± 1.0 | 1.8 ± 2.0 | <.0001 |
| Cesarean delivery, n (%) | 178 (57) | 107 (41) | 268 (93) | 58 (98) | 27 (71) | 22 (60) | <.0001 |
| Received optimal antenatal corticosteroids, n (%) | 138 (45) | 114 (44) | 195 (68) | 32 (54) | 14 (37) | 19 (51) | <.0001 |
| Male newborn, n (%) | 178 (60) | 149 (58) | 145 (51) | 33 (56) | 22 (61) | 24 (67) | .2531 |
| Primary reason for delivery, n (%) | | | | | | | <.0001[a] |
| Spontaneous labor | 171 (55) | 228 (87) | 0 | 2 (4) | 11 (29) | 21 (57) | |
| Preeclampsia | 0 | 0 | 219 (76) | 3 (5) | 0 | 0 | |
| Fetal heart rate nonreassuring | 54 (17) | 15 (6) | 49 (17) | 42 (72) | 7 (18) | 6 (16) | |
| Chorioamnionitis | 54 (17) | 12 (6) | 0 | 0 | 0 | 5 (14) | |
| Bleeding | 18 (6) | 6 (2) | 8 (3) | 0 | 20 (53) | 1 (3) | |
| Other | 13 (4) | 2 (1) | 12 (4) | 12 (20) | 0 | 4 (11) | |

*P* value column is based on $\chi^2$ or the Fisher exact test ([a]) for categorical variables and Kruskal-Wallis test for continuous variables.

*P* value tests for statistical significance across all 6 groups are shown.

*IUGR*, intrauterine fetal growth restriction; *PPROM*, preterm prelabor rupture of membranes; *PTL*, preterm labor; *SD*, standard deviation.

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neonatal serious morbidity, removing the variable with the highest *P* value and keeping in variables with a $P < .10$. The Hosmer-Lemeshow test was used to determine the goodness of fit of the final regression model. Statistical significance is defined as a $P < .05$; no adjustment is made for multiple comparisons.

## Sample size

For the sample size, we calculated the likelihood of at 10% difference between the rates of composite morbidity between those admitted for PTL and PPROM. Based on a previous study from these hospitals in babies < 34 weeks, the primary indications for premature delivery were PTL and PPROM were the most frequent reasons for admission and each accounted for about one-third of all the premature deliveries and the composite morbidity rate using for these 2 diagnoses was in excess of 60% and the mortality rate was 4%.[32] Given that the earlier gestational age chosen for the current study is <32 weeks, we conservatively assumed a composite morbidity rate of 70%. For a 10% difference in composite morbidity (assuming 80% power and 2-sided alpha = 0.05) at least 354 patients were needed in each group; thus, because the 2 predominant groups (PTL and PPROM) each compose about one-third of all patients, a total sample size of 1062 was determined.

## Results

The study was conducted from during a 2-year period and included deliveries that occurred from July 2013 to July 2015. We collected complete data on 1089 mother baby pairs. In the 1089 infants, the indications for admission to the obstetrical unit included PPROM, 310 (28.5%); preeclampsia, 288 (26.5%); PTL, 263 (24.2%); suspected intrauterine growth restriction (IUGR), 59 (5.4%); maternal vaginal bleeding not associated with placenta previa, 38 (3.5%); and short cervix, 37 (3.4%). Other less frequent reasons for maternal admission included abnormal fetal testing (abnormal fetal heart rate and/or biophysical profile), fetal anomalies, hydrops, isoimmunization, oligohydramnios, and chronic hypertension preceding pregnancy without preeclampsia. The indications for delivery were as follows: labor, 433 (39.8%); maternal disease (all other nonhypertensive diseases requiring delivery) and/or preeclampsia, 222 (20.4%); nonreassuring fetal status, 155 (14.2%); hemorrhage not associated with placenta previa, 49 (4.5%); and clinical chorioamnionitis, 49 (4.5%). Additional but infrequent indications for delivery included abruptio placentae, other maternal disease, infection detected by amniocentesis, PPROM/mature values on amniocentesis, placenta previa with bleeding, and umbilical cord prolapse. The admission and delivery characteristics for 6 major categories of reasons for admission and for the most frequent reasons for delivery are described in Tables 1 and 2.

Neonatal mortalities and morbidities by indication for admission and indication for delivery are shown in Tables 3 and 4. The primary outcome, comparing composite morbidity between the 2 major reason or admission groups of PTL (77.2%) and PPROM

**TABLE 3**
**Neonatal outcome by primary reason for admission**

| | PPROM (n = 310) | PTL (n = 263) | Preeclampsia (n = 288) | IUGR (n = 59) | Bleeding (n = 38) | Short cervix (n = 37) | *P* value |
|---|---|---|---|---|---|---|---|
| Composite morbidity | 227 (73)[a] | 203 (77)[a] | 221 (77) | 45 (76) | 28 (74) | 33 (89) | .3864 |
| Serious morbidity | 82 (27) | 68 (26) | 62 (22) | 20 (34) | 17 (45) | 20 (54) | <.0001 |
| Perinatal death | 32 (10) | 20 (8) | 17 (6) | 6 (10) | 5 (13) | 5 (14) | .2582 |
| Stillbirth | 5 | 0 | 2 | 0 | 0 | 1 | |
| Delivery room death | 5 | 6 | 2 | 0 | 2 | 0 | |
| Neonatal death | 22 | 14 | 13 | 6 | 3 | 4 | |
| Respiratory distress syndrome[b] | 206 (69) | 190 (74) | 211 (74) | 43 (73) | 23 (64) | 27 (75) | .5482 |
| On ventilator at 28 days of age[b] | 24/249 (10) | 28 (12) | 29 (11) | 14/54 (16) | 11/32 (34) | 10/32 (31) | <.0001 |
| Intraventricular hemorrhage grade 3 or 4[b] | 13 (4) | 19 (7) | 8 (3) | 1 (2) | 5 (14) | 8 (22) | <.0001[c] |
| Necrotizing enterocolitis[b] | 9 (3) | 15 (6) | 14 (5) | 3 (5) | 5 (14) | 2 (6) | .1090[c] |
| Periventricular leukomalacia[b] | 2 (1) | 1 (0.3) | 1 (0.3) | 1 (2) | 1 (3) | 0 | .213[c] |
| Sepsis[b] | 11 (4) | 5 (2) | 6 (2) | 2 (3) | 1 (3) | 1 (3) | .7065[c] |
| Cord arterial pH < 7.1[b] | 8 (3) | 7 (3) | 14 (5) | 2 (3) | 5 (14) | 0 | <.0001[c] |
| Cord venous pH < 7.1[b] | 5 (2) | 5 (2) | 9 (3) | 2 (3) | 3 (8) | 0 | .1891[c] |
| Arterial base excess <−12[b] | 5 (2) | 3 (1) | 6 (2) | 1 (2) | 2 (6) | 0 | .4776[c] |
| Venous base Excess <−12[b] | 2 (1) | 4 (2) | 5 (2) | 1 (2) | 2 (6) | 0 | .2599[c] |
| Five-minute Apgar score <5[b] | 24 (8) | 15 (6) | 15 (5) | 2 (3) | 2 (6) | 6 (17) | .1531[c] |
| Days in NICU, mean ± SD[b] | 61 ± 36 | 67 ± 38 | 64 ± 32 | 76 ± 41 | 85 ± 49 | 83 ± 40 | .0004 |

All values are n (%) except days in NICU.

*P* value column is based on $\chi^2$ or the Fisher exact test ([c]) for categorical variables, Kruskal-Wallis test for continuous variables.

*P* value tests for statistical significance across all 6 groups are shown.

*IUGR*, intrauterine fetal growth restriction; *NICU*, neonatal intensive care unit; *PPROM*, preterm prelabor rupture of membranes; *PTL*, preterm labor; *SD*, standard deviation.

[a] *P* = .2879 comparing PPROM vs PTL, test of the primary a priori hypothesis of the study; [b] Excludes those with stillbirth or death in delivery room.

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(73.2%), was not significantly different (*P* = .29). In univariable analyses, serious, but not composite, neonatal morbidity appeared to be more common in the group admitted for short cervix than in those admitted for PPROM, PTL, or preeclampsia (Table 3) and more common in those admitted for bleeding compared with those admitted for preeclampsia. These differences were not significant, however, in multiple logistic regression adjusting for gestational age at birth, route of delivery, and optimal use of antenatal corticosteroids. Other factors not directly related to the indications for maternal admission or delivery on regression analysis that affected neonatal composite and/or serious morbidity analysis included low 5-minute Apgar (odds ratio, 2.6; *P* = .045, 95% confidence interval [CI] 1.3 to 5.1) and a borderline significant positive impact of and optimal course of antenatal steroids (*P* =.07, 95% CI 0.5 to 1.0). None of the indications for admission or delivery adversely affected composite morbidity, and only suspected IUGR as an indication for admission and/or delivery was associated with a significantly increased rate of serious neonatal morbidity (*P* < .003) odds ratio, 4.5; 95% CI 2.1 to 9.8) (Table 5).

## Comment

### Principal findings

In this study, despite a substantial sample size and its prospective nature, we found no indications for obstetrical admission or indications for delivery that correlated with neonatal outcome in those delivered <32 weeks except for suspected IUGR. Few studies have evaluated the implications of the indications for hospital admission leading to premature delivery and the subsequent actual indication for the premature delivery and their relationship to neonatal outcome. Based on both the pathophysiology of many of these conditions as well as data from studies on individual complications, there are reasons to believe that these relationships might exist and have implications for counseling and management. Surprisingly, at least based on these considerations, we did not find any such differences except for confirming a relatively well-known

**TABLE 4**
**Neonatal outcome by primary reason for delivery**

| | Labor (n = 445) | Preeclampsia (n = 231) | NRFHRT (n = 207) | Evidence of infection (n = 73) | Bleeding (n = 65) | Other (n = 63) | *P* value |
|---|---|---|---|---|---|---|---|
| Composite morbidity, n (%) | 330 (74) | 176 (76) | 157 (76) | 60 (82) | 53 (82) | 50 (74) | .5991 |
| Serious morbidity, n | 118 (27) | 41 (18) | 77 (37) | 23 (32) | 18 (28) | 21 (31) | .0005 |
| Perinatal death | 31 (7) | 8 (4) | 36 (17) | 10 (14) | 6 (9) | 11 (16) | <.0001 |
| Stillbirth | 0 | 0 | 3 | 0 | 0 | 8 | |
| Delivery room death | 9 | 2 | 4 | 3 | 1 | 1 | |
| Neonatal death | 22 | 6 | 29 | 7 | 5 | 2 | |
| Respiratory distress syndrome[a] | 309 (71) | 170 (74) | 144 (72) | 48 (69) | 49 (77) | 39 (67) | .7714 |
| On ventilator at 28 days of age[a] | 49 (13) | 20 (9) | 26 (16) | 7 (12) | 12 (21) | 8 (15) | .1949 |
| Intraventricular hemorrhage grade 3 or 4[a] | 27 (6) | 6 (3) | 10 (5) | 9 (13) | 6 (9) | 1 (2) | .0133[b] |
| Necrotizing enterocolitis[a] | 22 (5) | 10 (4) | 9 (5) | 3 (4) | 4 (6) | 1 (2) | .9109[b] |
| Periventricular leukomalacia[a] | 6 (1) | 0 | 3 (2) | 1 (1) | 1 (2) | 0 | .3283[b] |
| Sepsis[a] | 9 (2) | 4 (2) | 7 (4) | 5 (7) | 2 (3) | 0 | .1240[b] |
| Cord arterial pH < 7.1[a] | 7 (2) | 8 (4) | 19 (10) | 2 (3) | 5 (8) | 2 (4) | .0002[b] |
| Cord venous pH < 7.1[a] | 5 (1) | 3 (1) | 13 (7) | 1 (1) | 4 (6) | 2 (4) | .0012[b] |
| Arterial base excess <−12[a] | 6 (1) | 2 (1) | 10 (5) | 1 (1) | 2 (6) | 1 (2) | .0501[b] |
| Venous base excess <−12[a] | 4 (1) | 1 (0.4) | 8 (4) | 0 | 3 (5) | 1 (2) | .0101[b] |
| Five-minute Apgar score <5[a] | 27 (6) | 9 (4) | 25 (13) | 5 (7) | 5 (8) | 3 (5) | .0266[b] |
| Days in NICU (mean ± SD) | 66 ± 37 | 66 ± 31 | 63 ± 41 | 67 ± 37 | 75 ± 48 | 67 ± 36 | .5938 |

All values are n (%) except days in NICU.

*P* value column is based on $\chi^2$ or the Fisher exact test ([b]) for categorical variables, Kruskal-Wallis test for continuous variables.

*P* value tests for statistical significance across all 6 groups are shown.

*NICU*, neonatal intensive care unit; *NRFHRT*, nonreassuring fetal heart rate tracing, *SD*, standard deviation.

[a] Excludes those with stillbirth or death in delivery room.

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relationship to adverse outcome and IUGR. As we have shown in a previous study[24] from a very similar population in the same gestational age range, IUGR imparts a marked increase in mortality and serious morbidity even when corrected for exposure to antenatal steroids, sex, and mode of delivery. We did not make any effort to confirm the diagnosis of IUGR after delivery because the intent of this study is to evaluate neonatal outcome based on the obstetrical diagnosis and the reasons for admission and delivery and not the impact of IUGR in the neonate, which is well established in the literature.

Other factors this study found to affect outcome included worse composite morbidity with earlier gestational age, low 5-minute Apgar and cesarean delivery, and a decreased composite morbidity with bleeding on admission and a borderline reduction with having received a complete course of antenatal corticosteroids. Other reasons for admission and delivery did not show any relationship to outcome when corrected for these factors. A few factors, such as low 5-minute Apgar and gestational age at delivery, would be expected. Increased morbidity with cesarean delivery is probably a marker for babies who required cesarean delivery for factors such as hypoxia and acidosis, which increase adverse outcome, and a lower morbidity with antenatal corticosteroids also is expected. The most surprising finding was the relationship between less morbidity among babies whose mothers were admitted for non-previa vaginal bleeding, a result that is counterintuitive and that we cannot explain.

## Comparison with other studies

The intent of the present study also was to study a large cohort but with very premature babies in whom complication rates are high and in whom the prospective collection of maternal data was thought to be more accurate and where both reasons for admission and reasons for delivery were analyzed. There are a number of studies that have revealed differences in outcome among babies delivered after abruptio placentae,[5-8] chorioamnionitis,[17,21-23,33] IUGR[24], and others, but very few are similar to

TABLE 5

**Logistic regression analysis of serious neonatal morbidity**

| | *P* value | Odds ratio | 95% Wald confidence limits |
|---|---|---|---|
| Preeclampsia | .4373 | 1.562 | 0.950–2.568 |
| Bleeding without previa | .5627 | 2.255 | 0.900–5.646 |
| Cervical shortening | .6152 | 1.494 | 0.588–3.792 |
| IUGR | .0034 | 4.536 | 2.092–9.836 |
| PPROM | .2945 | 1.491 | 0.920–2.415 |
| GA Delivery | <.0001 | 0.493 | 0.448–0.442 |
| Apgar < 5 | .0045 | 2.616 | 1.347–5.078 |

Reason for admission variables are relative to PTL.

Hosmer-Lemeshow goodness of fit $P = .3694$.

*GA*, gestational age; *IUGR*, intrauterine fetal growth restriction; *PPROM*, preterm prelabor rupture of membranes; *PTL*, preterm labor.

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the present study. Most of these studies of outcomes associated with individual complications, however, include babies of more advanced gestational age, and most did not evaluate the multiple other variables as we did in the present study.

Recently Delorme et al[34] from France performed a study on babies at 22–34 weeks and similar to this study found that only babies with IUGR had a greater risk of mortality than babies delivered due to other causes or reasons. Gagliardi et al[35] from Italy found similar results with greater rates of adverse neonatal outcomes with babies delivered due to "placentation disorders," which included hypertensive disorders and IUGR. Both studies, although prospective, focused on obtaining subjects from the birth of newborn rather than when the mother was admitted and the subsequently delivered prematurely, a subtle but important difference.

## Strengths and weaknesses

This is one of the only studies to comprehensively study the relationship of the indications for admission leading to premature delivery and the actual reasons for delivery and neonatal outcome. It is relatively large, prospective, with accurate information on demographics, indications for admission and delivery, delivery details and neonatal outcomes in a group of babies at 32 weeks or less at birth. Thus, it should be expected to reveal any substantial relationships between the inciting reasons for admission and delivery and neonatal outcome. The study further is geographically diverse and represents both teaching and private practice settings with a racial distribution fairly representative of the entire US population of babies who delivery prematurely.

The intent of the present study was to study a large cohort of very premature babies in whom complication rates are high and in whom the prospective collection of maternal data was thought to be more accurate and in whom both reasons for admission and reasons for delivery were analyzed. The latter point (ie, indication for admission), which has not been evaluated in any previous studies, is important because this is the information available to clinician at the time patient counseling occurs and often the ultimate reason the baby will deliver is not known at the time. Examples include PPROM, where labor or concern of fetal well-being or clinical chorioamnionitis may be the cause of delivery, or with vaginal bleeding and contractions, where similarly labor or bleeding or nonreassuring fetal status may lead to delivery. We believe this is one of the most compelling strengths of the study despite the negative results. The consistent difference in premature babies with increased adverse outcome with IUGR as shown in the previously mentioned studies and others is not unexpected and cannot be overemphasized from a clinical perspective.

This study does have some potential weaknesses. It is not clear why we were unable to show any correlation between some of the reasons for admission and delivery and adverse outcome beyond suspected IUGR. Certainly inadequate sample size for other complications beyond preterm labor and PPROM can explain the lack of apparent differences, as the study was powered only to show a difference in the most common reasons for admission and delivery. Perhaps another explanation was that by including only babies at or before 32 weeks at delivery, the impact of prematurity was so profound that any further differences imparted by these other reasons were obscured by fact that babies at these gestational ages have so many complications relating to prematurity alone. We considered doing a regression analysis of these indications taking gestational age out of the model, but this idea was not pursued because the gestational age is known and weighed into the counseling at the time the mother is admitted and or again when delivery is anticipated.

The indication for admission and/or delivery is only one of several factors taken into account when counseling the patient or anticipating the likelihood of complications. To an extent, we realized this issue in the study design by including the category of serious morbidity, because many of these very premature babies have RDS requiring ventilator therapy, and our serious category did not include RDS. This point is supported by the fact that IUGR affected only serious but not composite morbidity. It is also possible that a similar study of more advanced gestational ages might actually be more revealing of any contribution of the indications for admission and delivery to adverse outcome where gestational age has less of an impact on perinatal morbidity.

### Research implications

Beyond confirming the findings of this study as currently designed, or repeating it with a larger sample size, there are little more in the way further studies that this current one may suggest. As previously mentioned, perhaps there may be some implications of indications for admission and/or delivery on outcome in later gestational ages. But because these later gestational ages infrequently have serious morbidities, the need for intensive counseling is less furthermore the likelihood one could show such differences in a study would be difficult because the lower frequencies of the morbidities would require much larger sample sizes.

## Conclusion

Based on this and previous studies, patients with a variety indications for admission can be counseled similarly with regard to the likelihood of neonatal outcomes without requiring information to be tailored to the specific indication, and thus the counseling and management decisions can be based primarily on gestational age along with other factors, including estimated fetal weight, sex, race, plurality, and completion of a course of antenatal corticosteroids.[4] Only in the case of suspected IUGR do we have clear evidence that reasons for admission and delivery can be expected to affect outcome beyond these factors. ■

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