OBSTETRICS

Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort

Tracy A. Manuck, MD; Madeline Murguia Rice, PhD; Jennifer L. Bailit, MD, MPH; William A. Grobman, MD; Uma M. Reddy, MD, MPH; Ronald J. Wapner, MD; John M. Thorp, MD; Steve N. Caritis, MD; Mona Prasad, DO, MPH; Alan T. N. Tita, MD, PhD; George R. Saade, MD; Yoram Sorokin, MD; Dwight J. Rouse, MD; Sean C. Blackwell, MD; Jorge E. Tolosa, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network*

BACKGROUND: Although preterm birth <37 weeks' gestation is the leading cause of neonatal morbidity and mortality in the United States, the majority of data regarding preterm neonatal outcomes come from older studies, and many reports have been limited to only very preterm neonates. Delineation of neonatal outcomes by delivery gestational age is needed to further clarify the continuum of mortality and morbidity frequencies among preterm neonates.

OBJECTIVE: We sought to describe the contemporary frequencies of neonatal death, neonatal morbidities, and neonatal length of stay across the spectrum of preterm gestational ages.

STUDY DESIGN: This was a secondary analysis of an obstetric cohort of 115,502 women and their neonates who were born in 25 hospitals nationwide, 2008 through 2011. All liveborn nonanomalous singleton preterm (23.0-36.9 weeks of gestation) neonates were included in this analysis. The frequency of neonatal death, major neonatal morbidity (intraventricular hemorrhage grade III/IV, seizures, hypoxic-ischemic encephalopathy, necrotizing enterocolitis stage II/III, bronchopulmonary dysplasia, persistent pulmonary hypertension), and minor neonatal morbidity (hypotension requiring treatment, intraventricular hemorrhage grade I/II, necrotizing enterocolitis stage I, respiratory distress syndrome, hyperbilirubinemia requiring treatment) were calculated by delivery gestational age; each neonate was classified once by the worst outcome for which criteria was met.

RESULTS: In all, 8334 deliveries met inclusion criteria. There were 119 (1.4%) neonatal deaths. In all, 657 (7.9%) neonates had major morbidity, 3136 (37.6%) had minor morbidity, and 4422 (53.1%) survived without any of the studied morbidities. Deaths declined rapidly with each advancing week of gestation. This decline in death was accompanied by an increase in major neonatal morbidity, which peaked at 54.8% at 25 weeks of gestation. As frequencies of death and major neonatal morbidity fell, minor neonatal morbidity increased, peaking at 81.7% at 31 weeks of gestation. The frequency of all morbidities fell >32 weeks. After 25 weeks, neonatal length of hospital stay decreased significantly with each additional completed week of pregnancy; among babies delivered from 26-32 weeks of gestation, each additional week in utero reduced the subsequent length of neonatal hospitalization by a minimum of 8 days. The median postmenstrual age at discharge nadired around 36 weeks' postmenstrual age for babies born at 31-35 weeks of gestation.

CONCLUSION: Our data show that there is a continuum of outcomes, with each additional week of gestation conferring survival benefit while reducing the length of initial hospitalization. These contemporary data can be useful for patient counseling regarding preterm outcomes.

Key words: neonatal morbidity, neonatal mortality, prematurity

Introduction

Preterm delivery <37 weeks of gestation remains the leading cause of neonatal and childhood morbidity among nonanomalous infants in the United States and the developed world, and is the leading cause of death worldwide.[1-3] Recent advances in perinatal and neonatal medicine have resulted in substantial improvements in outcomes among premature infants.[4-6] A large study by the Neonatal Research Network found improvements in rates of death and major morbidity among neonates delivered at 23-24 weeks of gestation from 2009 through 2012, after outcomes had been relatively static from 1993 through 2008.[6] Despite this, rates of neonatal morbidity remain high, particularly among the most premature neonates. The majority of data regarding preterm neonatal death and morbidity come from older studies. Additionally, many studies have been limited to include only very preterm neonates, and frequently have focused on outcomes by birthweight cutoffs.[4,7-9] Outcomes by birthweight may be skewed by inclusion of more mature neonates with growth restriction.[4,8]

Gestational age at delivery is one of the major determinants of neonatal survival and morbidity. Clinicians and researchers commonly classify women with preterm birth (PTB) as delivering early preterm or late preterm. Early PTB is typically regarded as delivery <32 or 34 weeks of gestation, while those delivering 34-36 weeks of gestation are considered to have late PTB. Although these designations are somewhat arbitrary, grouping women into PTB delivery epochs may help facilitate research and clinical prevention strategies. Indeed, women presenting with symptoms of preterm labor <34 weeks have been treated more aggressively with corticosteroids and tocolysis, whereas those with the same symptoms >34 weeks generally have not received these interventions. Additionally, previous research has suggested that the etiologies

Cite this article as: Manuck TA, Rice MM, Bailit JL, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol 2016;215:103.e1-14.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2016.01.004

of PTB likely vary by gestational age, with those of later PTB being much more heterogeneous.[10,11]

Indeed, infants delivered at the earliest gestational ages are at highest risk for adverse outcomes during the neonatal period and beyond, as effects of prematurity may persist through childhood and adolescence.[7,12,13] In contrast, although infants delivered 34-36 weeks of gestation comprise the largest subset of preterm babies (~75%), they generally have a more benign course compared to their early preterm counterparts. However, late preterm infants continue to have an increased frequency of both immediate and long-term morbidity and mortality compared with term neonates.[14-17]

Limited evidence-based interventions to improve outcomes in the late preterm cohort exist, although studies are underway to assess efficacy of treatments traditionally reserved for earlier neonates (eg, antenatal corticosteroid administration). Delineation of neonatal outcomes by delivery gestational age is needed to further clarify the continuum of mortality and morbidity frequencies among preterm neonates.

Thus, this study was designed to describe the contemporary frequencies of neonatal death, major and minor neonatal morbidity, and neonatal length of hospital stay across the spectrum of preterm gestational ages (23-36 weeks of gestation) in singletons. We also sought to describe cause of neonatal death across different preterm gestational ages.

Materials and Methods

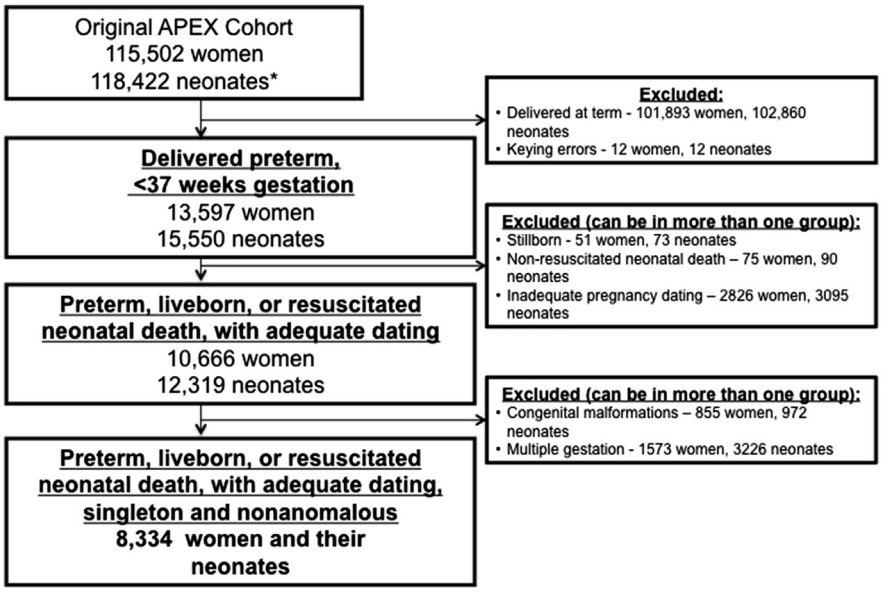
This is a secondary analysis of the previously described *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Assessment of Perinatal Excellence (APEX) obstetric cohort.[18,19] Briefly, the APEX study was an observational study designed to assist in the development of quality measures for intrapartum obstetric care. Patients eligible for data collection were those who were at least 23 weeks of gestation, had a live fetus on admission and delivered during the 24-hour period of randomly selected days representing one third of deliveries at 25 hospitals nationwide from 2008 through 2011; the main study included 115,502 women. Infants were followed up until discharge or 120 days of age, whichever came first. Institutional review board approval was obtained at each participating institution under a waiver of informed consent. This secondary analysis was reviewed by the University of Utah Institutional Review Board and deemed exempt.

For the purposes of this secondary analysis, we included all liveborn, nonanomalous singleton neonates delivered 23-36 weeks of gestation. Gestational age was determined by best obstetrical estimate available at the time of admission. Women with inadequate pregnancy dating (eg, pregnancies dated by last menstrual period only [without ultrasound confirmation] or by third trimester ultrasound only) were excluded. Neonates who were not resuscitated and died in the delivery room were excluded (ie, only neonates offered a trial of life were included).

The primary outcomes were neonatal death, major neonatal morbidity (intraventricular hemorrhage grade III or IV, seizures, hypoxic ischemic encephalopathy, necrotizing enterocolitis stage II or III, bronchopulmonary dysplasia, or persistent pulmonary hypertension), and minor neonatal morbidity (hypotension requiring treatment, intraventricular hemorrhage grade I or II, necrotizing enterocolitis stage I, respiratory distress syndrome, and/or hyperbilirubinemia requiring treatment) during the initial hospitalization. Each neonate was categorized into the most severe category for which they met criteria (death, major or minor morbidity). Those without any of the aforementioned morbidities were considered to have no neonatal morbidity.

We also examined presumed cause of death among neonates who died during the initial hospitalization. Research staff reported the cause or causes of death for each neonate as applicable if available in the neonate's chart. We grouped suspected causes of death into general classifications for the purposes of

FIGURE
Study inclusion



APEX, Assessment of Perinatal Excellence.

Manuck et al. Preterm neonatal morbidity and mortality. Am J Obstet Gynecol 2016.