OBSTETRICS

Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids

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BACKGROUND: Antenatal corticosteroids are given primarily to induce fetal lung maturation but results from meta-analyses of randomized controlled trials have not shown mortality or pulmonary benefits for extremely preterm infants although these are the infants most at risk of mortality and pulmonary disease.

OBJECTIVE: We sought to determine if exposure to antenatal corticosteroids is associated with a lower rate of death and pulmonary morbidities by 36 weeks' postmenstrual age.

STUDY DESIGN: Prospectively collected data on 11,022 infants 22 0/7 to 28 6/7 weeks' gestational age with a birthweight of ≥401 g born from Jan. 1, 2006, through Dec. 31, 2014, were analyzed. The rate of death and the rate of physiologic bronchopulmonary dysplasia by 36 weeks' postmenstrual age were analyzed by level of exposure to antenatal corticosteroids using models adjusted for maternal variables, infant variables, center, and epoch.

RESULTS: Infants exposed to any antenatal corticosteroids had a lower rate of death (2193/9670 [22.7%]) compared to infants without exposure (540/1302 [41.5%]) (adjusted relative risk, 0.71; 95% confidence interval, 0.65—0.76; $P < .0001$). Infants exposed to a partial course of antenatal corticosteroids also had a lower rate of death (654/2520 [26.0%]) compared to infants without exposure (540/1302 [41.5%]); (adjusted relative risk, 0.77; 95% confidence interval, 0.70—0.85; $P < .0001$). In an analysis by each week of gestation, infants exposed to a complete course of antenatal corticosteroids had lower mortality before discharge compared to infants without exposure at each week from 23-27 weeks' gestation and infants exposed to a partial course of antenatal corticosteroids had lower mortality at 23, 24, and 26 weeks' gestation. Rates of bronchopulmonary dysplasia in survivors did not differ by antenatal corticosteroid exposure. The rate of death due to respiratory distress syndrome, the rate of surfactant use, and the rate of mechanical ventilation were lower in infants exposed to any antenatal corticosteroids compared to infants without exposure.

CONCLUSION: Among infants 22-28 weeks' gestational age, any or partial antenatal exposure to corticosteroids compared to no exposure is associated with a lower rate of death while the rate of bronchopulmonary dysplasia in survivors did not differ.

Key words: antenatal corticosteroids, bronchopulmonary dysplasia, infant, intracranial hemorrhage, mechanical ventilation, morbidity, mortality, necrotizing enterocolitis, neonatal, newborn, patent ductus arteriosus, periventricular leukomalacia, pneumothorax, preterm, pulmonary, pulmonary hemorrhage, respiratory distress syndrome, respiratory support, sepsis, surfactant

Introduction

The effects of antenatal corticosteroids on mortality and pulmonary outcomes at the lowest gestations show mixed results, in part due to the small sample size of randomized controlled trials.[1,2] Although antenatal corticosteroids are given primarily to induce pulmonary maturity, induce surfactant release, and decrease respiratory distress syndrome, randomized controlled trials and meta-analyses of antenatal corticosteroids show no reduction in respiratory distress syndrome or neonatal death for infants delivered <30 weeks' gestation.[1,2] In addition, there are limited data from observational studies comparing the pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids to those without exposure because these studies have not been focused on pulmonary outcomes.[3-8] Extremely preterm infants who die <36 weeks' postmenstrual age cannot be assessed for the development of bronchopulmonary dysplasia, a type of chronic lung disease that is diagnosed at 36 weeks' postmenstrual age.[9] It is important to evaluate the competing outcomes of bronchopulmonary dysplasia and death both together and separately. Antenatal corticosteroid exposure may affect both outcomes for example if more infants survive following exposure and then develop bronchopulmonary dysplasia subsequently.

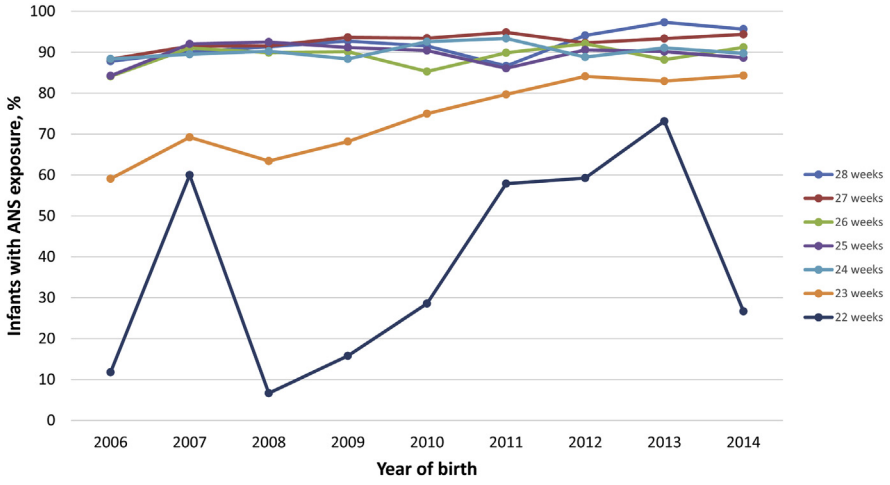
A complete course of antenatal corticosteroids is defined as 2 intramuscular doses of betamethasone given 12-24 hours apart or 4 intramuscular doses of dexamethasone given 12 hours apart.[10] Many preterm infants are born prior to the administration of a complete course of antenatal corticosteroids.[11,12] There are insufficient data on mortality and pulmonary outcomes of extremely preterm infants born after exposure to either a complete or a partial course of antenatal corticosteroids. We hypothesized that the rates of death would be

Cite this article as: Travers CP, Carlo WA, McDonald SA, et al. Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids. Am J Obstet Gynecol 2018;218:130.e1-13.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2017.11.554

FIGURE 1
Frequency of antenatal corticosteroids exposure by gestational age and year



Frequency of exposure to antenatal corticosteroids (ANS) by gestational age and year of birth. Administration of ANS increased over study period but remained lower at lower gestational ages.

Travers et al. Antenatal corticosteroid exposure and extremely preterm infant outcomes. Am J Obstet Gynecol 2018.

lower in infants exposed to antenatal corticosteroids. In addition, we hypothesized that the rates of physiologic bronchopulmonary dysplasia or death would be lower in infants exposed to antenatal corticosteroids. This study was also designed to determine if exposure to a partial or a complete course of antenatal corticosteroids is associated with improved survival and pulmonary outcomes in extremely preterm infants.

Materials and Methods

This was a hypothesis-driven study using data collected prospectively for the Neonatal Research Network Generic Database and follow-up studies. These data included infants 22 0/7 to 28 6/7 weeks' gestation with a birthweight of ≥401 g born from Jan 1, 2006, through Dec. 31, 2014, at any of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers. Maternal and neonatal sociodemographic and clinical data were collected from medical records by trained research personnel. Gestational age was determined by best obstetric estimate over best neonatal estimate.[13] Infants with congenital anomalies were included if they were resuscitated as these infants were less likely to have lethal anomalies. Infants who died in the first 12 hours after birth without delivery room resuscitation were excluded from the primary analysis to ensure that results were not affected by planned restriction of care but were included in a secondary analysis. The study protocol was approved by each center's institutional review board. ClincalTrials.gov identifiers are: NCT00063063 (generic database) and NCT00009633 (follow-up study).

Definitions

Infants were considered exposed to antenatal corticosteroids if their mother had received ≥1 doses of either betamethasone or dexamethasone.[10] Mothers were considered to have received a complete course if they had received at least 2 doses and 24 hours had passed from the time the first dose of antenatal corticosteroids was given. Data on repeat courses of antenatal corticosteroids were not collected.[14] Data were collected using standardized definitions until death or discharge. Follow-up data were collected using standardized definitions on eligible surviving infants at 18-22 months corrected gestational age. Bronchopulmonary dysplasia was defined based on respiratory support at 36 weeks' postmenstrual age using the physiologic definition, which uses an oxygen reduction challenge test among eligible infants.[15] The physiologic definition has been shown to be more reliable and precise than the clinical definition of bronchopulmonary dysplasia[15] (defined as supplemental oxygen at 36 weeks' postmenstrual age) and has been used by the Neonatal Research Network since 2006. All other outcomes were based on standardized definitions as per the generic database of the Neonatal Research Network.[16] Cause of death was defined as the underlying proximate disease that initiated the series of events leading to death based on both clinical evidence and autopsy findings where available.[13]

Statistical analysis

The primary outcome measure was death before discharge. A formal sample size and power estimate demonstrated that the sample size resulting from inclusion of all infants delivered from Jan. 1, 2006, through Dec. 31, 2014, would provide >95% power to detect an absolute difference of 4% centered around an overall event rate of 25%. All secondary outcome measures and analyses were prespecified. All outcomes were analyzed by level of exposure to antenatal corticosteroid: complete exposure, partial exposure, any (partial or complete) exposure, and no exposure. Differences in categorical variables were described using Fisher exact test. Kruskal-Wallis test was used for continuous skewed variables. Robust Poisson regression analysis was performed for factors present at birth associated with pulmonary outcomes including birthweight, sex, multiple births, small for gestational age (<10th centile), maternal variables (age, marital status, race, diabetes, rupture of membranes ≥24 hours, antepartum hemorrhage, and mode of delivery), center, and epoch (2006 through 2009, and 2010 through 2014).[17-19] There were 0.5% missing data for the primary outcome and 9.7% missing data for the follow-up outcomes at 18-22 months corrected gestational age. To ensure that results were not affected by missing data, multiple imputation analyses were