In-Hospital Outcomes in Large for Gestational Age Infants at 22-29 Weeks of Gestation

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Objective To estimate the risks of mortality and morbidities in large for gestational age (LGA) infants relative to appropriate for gestational age infants born at 22-29 weeks of gestation.

Study design Data on 156 587 infants were collected between 2006 and 2014 in 852 US centers participating in the Vermont Oxford Network. We defined LGA as sex-specific birth weight above the 90th centile for gestational age measured in days. Generalized additive models with smoothing splines on gestational age by LGA status were fitted on mortality and morbidity outcomes to estimate adjusted relative risks and their 95% CIs.

Results Compared with appropriate for gestational age infants, being born LGA was associated with decreased risks of mortality, respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, late-onset sepsis, severe retinopathy of prematurity, and chronic lung disease. Early onset sepsis and severe intraventricular hemorrhage were increased among LGA infants, but these risks were not homogeneous across the gestational age range.

Conclusions Being born LGA was associated with lower risks for all the examined outcomes except for early onset sepsis and severe intraventricular hemorrhage. *(J Pediatr 2018;■■:■■-■■).*

Infants born small for gestational age (SGA) are known to be at a high risk of mortality and morbidities.[1] Studies examining infants born at the opposite end of the spectrum, specifically large for gestational age (LGA) infants, have demonstrated increased risks for shoulder dystocia,[2] hypoglycemia,[2] lower 5-minute Apgar scores,[3] as well as a composite measure of neonatal morbidities[4] compared with appropriate for gestational age (AGA) infants. These studies, however, have been mainly restricted to infants born at term.[2-4] To the best of our knowledge, no studies to date have explored outcomes among extremely preterm LGA infants. Given their extreme prematurity, one would expect that a higher birth weight among these infants is advantageous. Understanding the associated benefits or risks at this opposite end of the spectrum is essential for improved management of outcomes.

Given the paucity of studies on outcomes of preterm LGA infants born at 22-29$^{6/7}$ weeks of gestation, we examined the risks of mortality and morbidities before initial hospital discharge comparing LGA with AGA infants using data on newborns from the Vermont Oxford Network (VON).[5]

Methods

We conducted a retrospective study on infants born between 154 days (22 weeks and 0 days) and 209 days (29 weeks and 6 days) of gestation at one of the 852 neonatal intensive care units located in the US or Puerto Rico and participating in the VON Very Low Birth Weight Database between January 1, 2006 and December 31, 2014. We excluded multiples and infants born with congenital malformations from our study population.[5] The University of Vermont's committee for human research approved the use of VON's deidentified research repository for this analysis.

Gestational age in days was estimated using obstetrical measures based on last menstrual period and prenatal ultrasound in the maternal chart, or if unavailable, a neonatologist's postnatal physical examinations.[6] An infant was defined as LGA if their

AGA	Appropriate for gestational age
CLD	Chronic lung disease
EOS	Early-onset sepsis
GAM	Generalized additive model
LGA	Large for gestational age
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome
RR	Relative risk
SGA	Small for gestational age
sIVH	Severe intraventricular hemorrhage
sROP	Severe retinopathy of prematurity
VON	Vermont Oxford Network

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birth weight was above the estimated 90th population percentile conditional on sex and days of gestation.[1] An infant was defined as AGA if their birth weight was less than the 90th but greater than the 10th population percentile conditional on sex and days of gestation.[1] We defined a binary variable for postnatal life support to indicate if an infant received any of the following: surfactant therapy at any time, endotracheal tube ventilation, ventilator support at any time (including nasal continuous positive airway pressure, nasal ventilation, face mask ventilation, or mechanical ventilation), epinephrine, or cardiac compressions.

Mortality was defined as death before hospital discharge. Infants born at VON participating centers and infants transferred from the reporting hospital to another hospital were tracked for survival status until ultimate disposition or the infant's first birthday, whichever came first.

Respiratory distress syndrome (RDS) was defined as room air PaO_2 <50 mm Hg, room air central cyanosis, supplemental oxygen to maintain PaO_2 >50 mm Hg, or supplemental oxygen to maintain a pulse oximeter saturation over 85%; and a chest radiograph consistent with RDS within the first 24 hours of life.[6] Patent ductus arteriosus (PDA) was defined as presenting 1 or more of the following: (1) left to right or bidirectional ductal shunt on Doppler echo or (2) systolic or continuous murmur; and 2 or more of the following: (1) hyperdynamic precordium, (2) bounding pulses, (3) wide pulse pressure, and (4) pulmonary vascular congestion, cardiomegaly, or both.[6] Necrotizing enterocolitis (NEC) was diagnosed at surgery or postmortem or required at least 1 clinical sign (eg, bilious gastric aspirate, abdominal distension, occult blood in stool) and at least 1 radiographic finding (eg, pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum).[6] NEC and bowel perforation were combined into 1 outcome labeled NEC. Early-onset sepsis (EOS; ≤day 3 of life) was defined as recovery of a bacterial pathogen from blood or cerebrospinal fluid.[6] Late-onset sepsis (LOS; >day 3 of life) was defined as recovery of a bacterial pathogen or coagulase negative Staphylococcus from blood or cerebrospinal fluid or recovery of a fungus from blood culture.[6] Severe intraventricular hemorrhage (sIVH) was defined as grades 3 or 4 using the Papile classification within 28 days of birth.[7] Severe retinopathy of prematurity (sROP) was defined as stages 3-5 based on a retinal examination before hospital discharge.[8] Chronic lung disease (CLD) was defined as continuous use of supplemental oxygen at 36 weeks of postmenstrual age or on oxygen at discharge at 34-35 weeks if transferred or discharged before 36 weeks.[6] The above morbidity outcomes were observed before initial hospital discharge.

Statistical Analyses

We computed summary statistics of maternal and neonatal characteristics for LGA and AGA infants. We also estimated the proportion of infants who received postnatal life support at each day of gestational age, separately for LGA and AGA infants. The estimates and 95% CIs were obtained using a normal generalized additive model (GAM) with a thin plate spline term on gestational age by LGA status.[9] We constrained the estimates to the unit interval by first fitting the model on the logit scale and then back-transforming the estimates with the logistic function.

We subsequently calculated (1) adjusted mortality and morbidity relative risks (RRs) and 95% CIs among LGA and AGA infants; (2) mortality and morbidity rates among LGA and AGA infants by gestational days; (3) unadjusted RRs and 95% CIs for mortality and morbidities among LGA and AGA infants by gestational days; and (4) adjusted RRs and 95% CIs for mortality and morbidities among LGA and AGA infants by gestational days.

Adjusted RRs (a) were estimated using standard Poisson regression. Mortality and morbidity rates (b), unadjusted RRs (c), and adjusted RRs (d) were estimated via, respectively, normal, Poisson, and binomial GAMs with thin plate spline terms on gestational age by LGA status. The regression models in (a) and (d) were adjusted for the following variables: prenatal care (yes, no), antenatal corticosteroids (yes, no), maternal race/ethnicity (Black, Hispanic, White, Asian, other), newborn sex (male/female), and postnatal life-support (yes, no). In addition, the regression models in (a) were adjusted for gestational age in days. We tested the interaction between LGA and antenatal corticosteroids. Because this was not significant for any of the outcomes, it was not subsequently included in any of the regression models defined above. Analyses were performed using R[10] and SAS v 9.4 (SAS Institute, Cary North Carolina). GAMs were fitted using the R package mgcv.[9]

We conducted an analysis to assess the sensitivity of the results to the exclusion of infants with a birth weight above the 97th percentile for gestational age[11] as these infants might have had an underestimated gestational age.

Results

The overall sample size was 156 587 infants of which 15 694 (10.0%) were classified as LGA (9.0% at 22 weeks; 9.4% at 23; 10.1% at 24; 10.0% at 25; 10.0% at 26; 10.0% at 27; 10.0% at 28; 10.2% at 29 weeks). After excluding SGA infants, the sample size available for analysis was 141 006 infants. Compared with mothers of AGA infants, mothers of LGA infants were less likely to have had hypertension (9.8% vs 26.0%) and cesarean delivery (52.7% vs 62.9%) but were slightly more likely to have had chorioamnionitis (21.5% vs 19.3%) (**Table I**). This is also shown in **Figure 1**, A (available at www.jpeds.com) where the rates of chorioamnionitis are higher among LGA infants, especially at later gestational ages between 27 and 29 weeks of gestation. Moreover, **Figure 1**, B shows hypertension rates that are similar between the 2 groups until around week 24 which then increase more rapidly for AGA infants between 24 and 29 weeks of gestation. As expected, LGA infants had higher birth weights, larger head circumferences, and less frequent low admission temperatures <36.5°C (34.9% vs 46.8%) than AGA infants (**Table I**).

Postnatal life support was more likely to be delivered to LGA than AGA infants at lower gestational ages. At day 154 (22 weeks), the rate of life support interventions received by LGA

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