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Outcomes of Small for Gestational Age Infants < 27 Weeks' Gestation

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Abstract

Objective—To determine whether small for gestational age (SGA) infants <27 weeks gestation is associated with mortality, morbidity, growth and neurodevelopmental impairment at 18–22 months' corrected age (CA).

Study design—This was a retrospective cohort study from National Institute of Child Health and Human Development Neonatal Research Network's Generic Database and Follow-up Studies. Infants born at <27 weeks' gestation from January 2006 to July 2008 were included. SGA was defined as birth weight <10th percentile for gestational age by the Olsen growth curves. Infants with birth weight 10th percentile for gestational age were classified as non-SGA. Maternal and infant characteristics, neonatal outcomes and neurodevelopmental data were compared between the groups. Neurodevelopmental impairment was defined as any of the following: cognitive score <70 on BSID III, moderate or severe cerebral palsy, bilateral hearing loss (+/- amplification) or blindness (vision <20/200). Logistic regression analysis evaluated the association between SGA status and death or neurodevelopmental impairment.

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Results—There were 385 SGA and 2586 non-SGA infants. Compared with the non-SGA group, mothers of SGA infants were more likely to have higher level of education, prenatal care, cesarean delivery, pregnancy-induced hypertension and antenatal corticosteroid exposure. SGA infants were more likely to have postnatal growth failure, a higher mortality and to have received prolonged mechanical ventilation and postnatal steroids. SGA status was associated with higher odds of death or neurodevelopmental impairment [OR 3.91 (95% CI: 2.91–5.25), $P < 0.001$].

Conclusion—SGA status among infants <27 weeks' gestation was associated with an increased risk for postnatal steroid use, mortality, growth failure and neurodevelopmental impairment at 18–22 months' CA.

Keywords

extremely preterm infants; neurodevelopmental follow-up

Extreme prematurity and growth restriction are risk factors for death and adverse neonatal outcomes.[1, 2] In the 1970's, SGA preterm infants were noted to be at lower risk for respiratory distress syndrome (RDS) and intracranial hemorrhage (ICH).[3] It was then proposed that these infants had accelerated pulmonary maturation as a response to intrauterine stress.[3, 4] In 2000, the Vermont Oxford Network study on very low birth weight (VLBW) infants with birth weights (BW) <10th percentile for gestation showed significantly higher odds of death, necrotizing enterocolitis (NEC) and RDS compared with appropriate for gestational age (AGA) infants.[5] Similarly, Simchen et al noted that growth restriction was not protective against adverse neonatal outcomes and that SGA preterm infants were at higher risk for mortality and infection when compared with AGA preterm infants.[6]

In addition to the risk of death and adverse neonatal outcomes,[5–7] preterm SGA infants may also be at greater risk for neurodevelopmental impairment later in life.[8, 9] Morsing et al demonstrated that SGA infants born between 24 and 29 weeks gestation had increased risk of cognitive impairment than AGA preterm infants at 5–8 years of age.[10] In the EIPAGE study, infants born between 29 to 32 weeks' gestation with BWs <10th percentile were more likely to have cognitive and behavioral problems at school age; however, this was not observed for survivors born at 24 to 28 weeks that had BWs <10th percentile.[11] Many studies on preterm SGA infants are limited by small sample size and have shown conflicting results regarding neonatal and long-term neurodevelopmental outcomes. Furthermore, growth restriction during fetal life resulting in SGA status has been associated with later onset of childhood and adult disease.[12] Thus, investigation of risk factors and long term health outcomes associated with SGA status among preterm infants is important. We hypothesized that SGA infants <27 weeks' gestation are at higher risk for morbidity and mortality during the initial hospitalization and growth and neurodevelopmental impairment at 18–22 months' CA compared with non-SGA infants. The objectives of this study were to: (1) determine the incidence and risk factors associated with SGA among infants born between 23 weeks to 26 6/7 weeks' gestation; (2) compare the risk of mortality and morbidities among SGA and non-SGA preterm infants; and (3) compare growth and neurodevelopmental outcomes at 18–22 months' CA among SGA and non-SGA infants born at <27 weeks GA.

Methods

This study was a retrospective cohort analysis of prospectively collected data from the National Institute of Child Health and Human Development Neonatal Research Network's (NRN) Generic Database and Follow-up Studies. Infants born in one of the participating NRN sites between January 2006 to July 2008, were included if they were born between 23

weeks to 26 6/7 weeks of gestation. Infants with major congenital anomalies or syndromes and those who declined neurodevelopmental follow-up were excluded from the study. Trained research personnel collected socio-demographic and clinical data from birth up to death or discharge. The timing and causes of death were included in the data collection. Each center's Institutional Review Board approved the study and data collection procedures.

BW percentiles were assessed based on the GA of the infant. GA was determined in the following order: (1) best obstetrical estimate which was based on the last menstrual period, obstetrical variables and/or early prenatal ultrasound; and (2) best neonatologist estimate based on the Ballard scoring. Definition of SGA was a BW of <10th percentile for GA based on the sex-specific Olsen growth curves.[13] Infants with BW 10th percentile for GA were defined as non-SGA. Information on neonatal morbidity was collected at death or discharge, or at 120 days, whichever occurred first. Weight, length, and head circumference were recorded at 36 weeks' postmenstrual age (PMA) and at 18–22 month follow up visit; and were plotted on the Olsen growth curves [13] and the WHO growth charts [14] respectively. Postnatal growth failure was defined as either weight or length <10th percentile for age. All surviving infants were invited to participate in a follow-up visit at 18–22 months' corrected age (CA). During the follow-up visit, a comprehensive neurodevelopmental assessment [15] that included a neurologic examination and the Bayley Scales of Infant and Toddler Development (BSID) III [16] was performed by certified examiners trained to reliability.

The primary outcome of the study was the risk of death or neurodevelopmental impairment. Neurodevelopmental impairment was defined as presence of at least one of the following: 1) a score of <70 on the cognitive component of the BSID III, 2) moderate or severe cerebral palsy (CP) based on the gross motor functional classification system (GMFCS)[17], 3) presence of bilateral hearing loss (+/- amplification) or bilateral blindness (vision <20/200). Secondary outcomes included were the following: cognitive scores <80 and language scores on the BSID III, morbidities associated with prematurity, duration of total parenteral nutrition, length of hospital stay, and presence of growth failure at 36 weeks PMA and at 18–22 months' CA.

Statistical Analyses

The study cohort consisted of SGA and non-SGA infants based on the Olsen growth curves. Infants who survived to NICU discharge but were lost to follow up at 18–22 months comprised the lost to follow-up group. Between group differences were compared using Chi-square or Fisher exact test for categorical variables and t-tests for continuous variables. A *p* value of < 0.05 was considered statistically significant. Baseline maternal and infant characteristics were compared between the lost to follow-up group and the study cohort; followed by analysis of similar baseline variables between the SGA and non-SGA groups. Descriptive statistics were used to characterize the growth and neurodevelopmental outcomes at 18–22 months' corrected age of the SGA and non-SGA groups. Covariate-adjusted analyses were conducted using multivariable logistic regression models that treated study center as a random effect. Risk factors present at birth were entered into these models to estimate the association of SGA status on the primary and secondary outcomes. The results were presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). Risk factors adjusted for in the model were the following: male sex, GA, antenatal corticosteroids use, multiple birth, maternal education and pregnancy-induced hypertension. These variables are important predictors of outcomes and were selected a priori based on previous studies on SGA preterm infants. Statistical analyses were performed using SAS statistical software version 9.2.

Results

The study population included 2,971 infants born between 23 0/7 and 26 6/7 weeks gestation with 385 SGA and 2,586 non-SGA infants (Figure; available at www.jpeds.com). Compared with the non-SGA group, mothers of infants in the SGA group were more likely to have received prenatal care and ANS, to have pregnancy-induced hypertension, and to have had a high school education. SGA infants were more likely to be delivered by cesarean delivery and to have a 5-minute Apgar score <5 (Table I). About one-half of the SGA infants also had head circumference (51%) and length (56%) <10th percentile at birth. Infants in the non-SGA group had higher rates of RDS and surfactant treatment, surgically-treated patent ductus arteriosus and grade III/IV ICH compared with the SGA group. SGA infants had higher rates of postnatal steroid use and had longer duration of mechanical ventilation and hospital stay (Table II). Rates of other morbidities were comparable between the two groups. The overall mortality was significantly higher in the SGA group compared with the non-SGA group (55.8% vs. 36.5%, $P < .001$). Among infants <24 weeks gestation, more SGA infants died due to immaturity and were offered comfort care only (29% vs. 18%, $p < .001$). Although the duration of total parenteral nutrition use were similar, SGA infants were more likely to have a slower weight gain velocity, growth failure and head circumference <10th percentile at 36 weeks PMA (Table II).

Of the 1,492 infants who survived and completed the 18–22 month follow-up visit, 150 infants were SGA and 1,342 infants were non-SGA. The follow-up rate was 82.3% for this study cohort (Figure). Mothers of infants lost to follow-up were less likely to have received prenatal care and ANS or to have pregnancy-induced hypertension. Infants lost to follow-up were less likely to be born via cesarean delivery or to have RDS and growth failure at 36 weeks PMA; but they were more likely to weigh more at birth and to have bronchopulmonary dysplasia (BPD), surgically-treated patent ductus arteriosus, grade III/IV ICH and cystic periventricular leukomalacia (data not shown).

Analysis of the growth and neurodevelopmental outcomes at the 18–22 month follow-up visit showed that SGA infants were more likely to have growth failure, head circumference <10th percentile, blindness, moderate to severe CP and cognitive scores <80 on the BSID III compared with the non-SGA group (Table III; available at www.jpeds.com). After adjusting for study center and risk factors present at birth in the regression model, SGA status remained significantly associated with death or neurodevelopmental impairment at 18–22 months' CA with an adjusted OR [95% CI] of 3.91 [2.91–5.25] (Table IV).

Discussion

SGA infants born between 23 and 26 6/7 weeks gestation were compared with those infants whose BW was 10th percentile using the Olsen growth curves.[13] There was a significantly higher rate of maternal pregnancy-induced hypertension in the SGA group compared with mothers in the non-SGA group. Non-SGA infants had higher rates of neonatal morbidities such as RDS, surgically-treated patent ductus arteriosus and grade III/IV ICH; and SGA infants had a higher rate of postnatal steroid use and required longer duration of mechanical ventilation and hospitalization. In spite of lower prematurity associated morbidities, SGA infants had significantly higher risks of death, postnatal growth failure and neurodevelopmental impairment at 18–22 months' CA compared with non-SGA infants (regardless of adjustment for ANS and maternal education).

Based on Olsen growth curves published in 2010, our frequency of SGA infants was 13% among the 2,971 infants studied. Growth curves generated from a population that may no longer be representative of the current population of extremely preterm infants may lead to

confusing results when analyzing the association of SGA status and neonatal outcomes. In a separate analysis using the Alexander growth curves,[18] the frequency of SGA infants for our cohort was calculated to be 6% instead of 13% and 208 infants would have been misclassified as non-SGA. Infants of higher birth orders were also plotted on the Olsen growth curves because the intrauterine growth of singleton, twins, and triplets are similar up to ~28 to 30 weeks gestation.[18, 19]

Although several studies on outcomes of SGA infants have been published, there is difficulty in delineating the true effects of SGA status on neonatal morbidities and long term outcomes due to comparison of SGA infants with other preterm infants that were matched for birth weight and not for their GA. Claas et al evaluated neonatal outcomes of 81 AGA and 98 SGA preterm infants with BW of 750g; and found that AGA preterm infants had a higher risk for RDS and severe intraventricular hemorrhage (IVH) compared with the SGA infants.[9] However, the population of AGA infants in this study were of much younger GA than the SGA group with mean GA of 26.3 weeks vs. 28.5 weeks.[20] Bardin et al studied 37 SGA and 147 AGA preterm infants and showed no difference in the risk of death and RDS.[21] Simchen et al demonstrated that SGA infants born at 27 to 32 weeks gestation had higher rates of death and culture-proven sepsis compared with AGA preterm infants; however, no difference in the incidence of IVH was found.[6] In addition to limited sample size, some studies have selected a wider range of preterm infants that may not have completely addressed the issue of SGA status among the extremely preterm infants.

The rate of BPD was similar between the two groups in this study, however, SGA infants remained on mechanical ventilation longer and received postnatal steroid more often than non-SGA infants. We speculate that aside from their respiratory status, SGA infants may have received a longer duration of mechanical ventilation in view of their smaller body mass and the high caloric expenditure associated with work of breathing among premature neonates. Because we do not have a standardized protocol regarding postnatal steroid use among the centers of the NRN, we were unable to explain why postnatal steroid use was significantly higher in the SGA group. Similar to previous report, ANS exposure was more common among SGA infants and this may explain the lower incidence of severe ICH compared with the non-SGA group.[22] Rates of late-onset sepsis/meningitis, NEC, and cystic periventricular leukomalacia were comparable between the two groups of infants. A higher mortality rate among the SGA group may explain the lack of association with other morbidities, because they did not survive long enough to develop these problems. In addition to a higher mortality rate, there were also more SGA infants that died without intensive care treatment. It is possible that the combination of extreme prematurity and growth restriction have led to a decision of a non-aggressive approach in the management of these infants.

Many studies reporting on growth and neurodevelopmental outcomes of SGA infants have shown conflicting results due to limited numbers of survivors at follow-up. In the EPIPAGE study, SGA status was not significantly associated with CP, school difficulties, or cognitive and behavioral problems among preterm infants born at 24 to 28 weeks gestation.[11] Latal-Hajnal et al noted that SGA status among 219 VLBW infants studied did not confer worse neurodevelopmental outcome; however, SGA infants with catch-up weight <10th percentile by two years of age had lower mean (SD) psychomotor developmental index compared with SGA infants with catch-up weight >10th percentile [89.9 (17.4) vs. 101.8 (14.5)].[23] Our study demonstrated that SGA infants were at higher risk for postnatal growth failure and neurodevelopmental impairment at 18–22 months' CA. Mothers of SGA infants had significantly higher rates of prenatal care and had more years of education; and despite adjusting for other predictors at birth in the analysis, SGA infants remained at higher risk for death or neurodevelopmental impairment at 18–22 months' CA compared with their AGA

counterparts. A more frequent use of neonatal treatments that may result in adverse long-term outcomes such as postnatal steroid,[24] may have contributed to a higher rate of death and neurodevelopmental impairment among the SGA group. The higher rate of postnatal steroid use in the SGA group may have counteracted the beneficial effect of ANS exposure [25, 26] on death and neurodevelopmental impairment.

Currently, there is growing evidence to support that there are neurologic and behavioral adverse effects of fetal growth restriction among SGA preterm infants. A study on 36 sets of SGA extremely low birth weight twins/triplets and their AGA twin/triplet siblings showed SGA infants remained smaller in size and had more behavioral, speech and visual problems at school age despite being raised in the same environment compared with their AGA twin/triplet.[27] In sheep models with growth restriction in the latter half of gestation, growth-restricted lambs have decreased myelination, which can affect the conduction velocity of axons and potentially compromise neural function.[28] Inder et al demonstrated that VLBW infants with intrauterine growth restriction were not protected from moderate or severe white matter abnormality on magnetic resonance imaging (MRI) after adjusting for GA and mode of delivery.[29] A brain MRI study by Tolsa et al of 28 preterm infants (half with placental insufficiency and BW <10th percentile) showed significantly reduced intracranial volume and cerebral cortical gray matter both at two weeks of age and at term equivalent, compared with the matched AGA preterm infants.[30]

There are limitations to our study. We had a lost to follow-up rate of 17% at the 18–22 month visit. The use of 10th percentile as the cut-off may not have been the optimal cut-off point to distinguish important differences in outcomes between the two groups of infants. Further investigations using other percentiles should be done to delineate the true effects of SGA status among these high risk infants. Our study focused on SGA status at birth; we do not have detailed information on the cause of growth restriction during pregnancy that resulted in the SGA status. The strengths of this study are the large and diverse group of high risk infants and the participation of multiple academic centers. The use of the Olsen growth curves to determine the SGA status at birth is unique and has not been used previously to determine the short and longer term health outcomes of SGA preterm infants.

In conclusion, our findings support the concept that SGA status at birth confers an additional hazard to survival, growth and neurodevelopmental outcome in extremely preterm infants. This information should be considered during antenatal or postnatal discussions with parents when an extremely preterm infant is SGA. In addition, the importance of long term follow-up should be emphasized to families at discharge with early referral to special services if neurodevelopmental impairment is detected. Lastly, optimal nutrition and close supervision of all growth variables are important, as SGA infants are also at risk for postnatal growth failure which can negatively impact their neurodevelopment.

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Abbreviations

AGA	appropriate for gestational age
BPD	bronchopulmonary dysplasia
BSID	Bayley scale of infant development
ICH	intracranial hemorrhage
NEC	necrotizing enterocolitis
RDS	respiratory distress syndrome
ROP	Retinopathy of prematurity
SGA	Small for gestational age

References

1. Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. *BMJ*. 1999; 319:1093–7. [PubMed: 10531097]
2. Kamoji VM, Dorling JS, Manktelow BN, Draper ES, Field DJ. Extremely growth-retarded infants: is there a viability centile? *Pediatrics*. 2006; 118:758–63. [PubMed: 16882834]
3. Procianny RS, Garcia-Prats JA, Adams JM, Silvers A, Rudolph AJ. Hyaline membrane disease and intraventricular haemorrhage in small for gestational age infants. *Arch Dis Child*. 1980; 55:502–5. [PubMed: 7436499]
4. Chiswick ML. Prolonged rupture of membranes, pre-eclamptic toxemia, and respiratory distress syndrome. *Arch Dis Child*. 1976; 51:674–9. [PubMed: 1036670]
5. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. *Am J Obstet Gynecol*. 2000; 182:198–206. [PubMed: 10649179]
6. Simchen MJ, Beiner ME, Strauss-Livathan N, Dulitzky M, Kuint J, Mashiach S, et al. Neonatal outcome in growth-restricted versus appropriately grown preterm infants. *Am J Perinatol*. 2000; 17:187–92. [PubMed: 11041440]
7. Evans N, Hutchinson J, Simpson JM, Donoghue D, Darlow B, Henderson-Smart D. Prenatal predictors of mortality in very preterm infants cared for in the Australian and New Zealand Neonatal Network. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92:F34–40. [PubMed: 16877475]
8. Spinillo A, Stronati M, Ometto A, Fazzi E, Lanzi G, Guaschino S. Infant neurodevelopmental outcome in pregnancies complicated by gestational hypertension and intra-uterine growth retardation. *J Perinat Med*. 1993; 21:195–203. [PubMed: 8229610]
9. Spinillo A, Gardella B, Preti E, Zanchi S, Stronati M, Fazzi E. Rates of neonatal death and cerebral palsy associated with fetal growth restriction among very low birthweight infants. A temporal analysis. *BJOG*. 2006; 113:775–80. [PubMed: 16753043]
10. Morsing E, Asard M, Ley D, Stjernqvist K, Marsal K. Cognitive function after intrauterine growth restriction and very preterm birth. *Pediatrics*. 2011; 127:e874–82. [PubMed: 21382944]
11. Guellec I, Lapillonne A, Renolleau S, Charaluk ML, Roze JC, Marret S, et al. Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction. *Pediatrics*. 2011; 127:e883–91. [PubMed: 21382951]
12. Shankaran S, Das A, Bauer CR, Bada H, Lester B, Wright L, et al. Fetal origin of childhood disease: intrauterine growth restriction in term infants and risk for hypertension at 6 years of age. *Arch Pediatr Adolesc Med*. 2006; 160:977–81. [PubMed: 16953023]
13. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics*. 2010; 125:e214–24. [PubMed: 20100760]
14. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl*. 2006; 450:76–85. [PubMed: 16817681]

15. Vohr BR, Stephens BE, Higgins RD, Bann CM, Hintz SR, Das A, et al. Are Outcomes of Extremely Preterm Infants Improving? Impact of Bayley Assessment on Outcomes. *J Pediatr*. 2012
16. Bayley, N. Bayley Scales of Infant and Toddler Development. 3. The Psychologic Corporation; San Antonio, TX: 2006. (Bayley-III)
17. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997; 39:214–23. [PubMed: 9183258]
18. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol*. 1996; 87:163–8. [PubMed: 8559516]
19. Blickstein I. Normal and abnormal growth of multiples. *Semin Neonatol*. 2002; 7:177–85. [PubMed: 12234742]
20. Claas MJ, Bruinse HW, van der Heide-Jalving M, Termote JU, de Vries LS. Changes in Survival and Neonatal Morbidity in Infants with a Birth Weight of 750 g or Less. *Neonatology*. 2010; 98:278–88. [PubMed: 20453522]
21. Bardin C, Zekowitz P, Papageorgiou A. Outcome of small-for-gestational age and appropriate-for-gestational age infants born before 27 weeks of gestation. *Pediatrics*. 1997; 100:E4. [PubMed: 9233975]
22. Lee BH, Stoll BJ, McDonald SA, Higgins RD. Adverse neonatal outcomes associated with antenatal dexamethasone versus antenatal betamethasone. *Pediatrics*. 2006; 117:1503–10. [PubMed: 16651303]
23. Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. *J Pediatr*. 2003; 143:163–70. [PubMed: 12970627]
24. Wilson-Costello D, Walsh MC, Langer JC, Guillet R, Laptook AR, Stoll BJ, et al. Impact of postnatal corticosteroid use on neurodevelopment at 18 to 22 months' adjusted age: effects of dose, timing, and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *Pediatrics*. 2009; 123:e430–7. [PubMed: 19204058]
25. Lee BH, Stoll BJ, McDonald SA, Higgins RD. Neurodevelopmental outcomes of extremely low birth weight infants exposed prenatally to dexamethasone versus betamethasone. *Pediatrics*. 2008; 121:289–96. [PubMed: 18245420]
26. Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *JAMA*. 2011; 306:2348–58. [PubMed: 22147379]
27. Monset-Couchard M, de Bethmann O, Relier JP. Long term outcome of small versus appropriate size for gestational age co-twins/triplets. *Archives of disease in childhood Fetal and neonatal edition*. 2004; 89:F310–4. [PubMed: 15210662]
28. Rees S, Inder T. Fetal and neonatal origins of altered brain development. *Early Hum Dev*. 2005; 81:753–61. [PubMed: 16107304]
29. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr*. 2003; 143:171–9. [PubMed: 12970628]
30. Tolsa CB, Zimine S, Warfield SK, Freschi M, Sancho Rossignol A, Lazeyras F, et al. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. *Pediatr Res*. 2004; 56:132–8. [PubMed: 15128927]

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women and Newborns (U10 HD40461) – Neil N. Finer, MD; Yvonne E. Vaucher, MD MPH; David Kaegi, MD; Maynard R. Rasmussen, MD; Kathy Arnell, RNC; Clarence Demetrio, RN; Martha G. Fuller, RN MSN; Wade Rich, BSHS RRT; Radmila West, PhD.

University of Iowa Children's Hospital (U10 HD53109; M01 RR59) – Michael J. Acarregui, MD; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA; Erin M. Reynolds, MPH.

University of Miami, Holtz Children's Hospital (U10 HD21397; M01 RR16587) – Shahnaz Duara, MD; Charles R. Bauer, MD; Ruth Everett-Thomas, RN MSN; Sylvia Hiriart-Fajardo, MD; Arielle Rigaud, MD; Maria Calejo, MS; Silvia M. Frade Eguaras, MA; Michelle Berkovits, PhD; Andrea Garcia, MA; Helina Pierre, BA; Alexandra Stoerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089; M01 RR997) – Kristi L. Watterberg, MD; Jean R. Lowe, PhD; Janell F. Fuller, MD; Robin K. Ohls, MD; Conra Backstrom Lacy, RN; Rebecca Montman, BSN; Sandra Brown, BSN

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521; UL1 RR24160; M01 RR44) – Dale L. Phelps, MD; Gary J. Myers, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN; Diane Hust, MS RN CS; Julie Babish Johnson, MSW; Rosemary L. Jensen, Emily Kushner, MA; Joan Merzbach, LMSW; Kelley Yost, PhD; Lauren Zwetsch, RN MS PNP.

University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital, and Lyndon Baines Johnson General Hospital/Harris County Hospital District (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia W. Evans, MD; Charles Green, PhD; Beverly Foley Harris, RN BSN; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; M. Layne Poundstone, RN BSN; Saba Siddiki, MD; Maegan C. Simmons, RN; Patti L. Pierce Tate, RCP; Sharon L. Wright, MT(ASCP).

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689; M01 RR633) – Pablo J. Sánchez, MD; Roy J. Heyne, MD; Walid A. Salhab, MD; Charles R. Rosenfeld, MD; Alicia Guzman; Melissa H. Leps, RN; Nancy A. Miller, RN; Gaynelle Hensley, RN; Sally S. Adams, MS RN CPNP; Linda A. Madden, RN CPNP; Elizabeth Heyne, PsyD PA-C; Janet S. Morgan, RN; Catherine Twell Boatman, MS CIMI; Lizette E. Torres, RN.

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124; M01 RR64; UL1 RR25764) – Roger G. Faix, MD; Bradley A. Yoder, MD; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN; Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RNC; Mike Steffen, PhD; Karen Zanetti, RN.

Wake Forest Baptist Medical Center, Forsyth Medical Center, and Brenner Children's Hospital (U10 HD40498; M01 RR7122) – T. Michael O'Shea, MD MPH; Robert G. Dillard, MD; Lisa K. Washburn, MD; Barbara G. Jackson, RN; BSN; Nancy Peters, RN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond,

MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Mary E. Johnson, RN BSN; Laura A. Goldston, MA.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871; UL1 RR24139; M01 RR125) – Richard A. Ehrenkranz, MD; Harris Jacobs, MD; Christine G. Butler, MD; Patricia Cervone, RN; Sheila Greisman, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Joanne Williams, RN BSN; Elaine Romano, MSN.

Figure 1.
Patient population. FU – follow-up, LTFU – lost to follow-up.

Table 1

Maternal and Infant Baseline Clinical Characteristics

	SGA n = 385		Non-SGA n = 2586		P-value
Maternal	Mean/h	SD/%	Mean/h	SD/%	
Maternal Age	27.1	6.2	26.8	6.4	0.39
African-American	151	40.1%	971	38.6%	0.59
Married Marital Status	181	47%	1129	43.7%	0.22
Education <high school [#]	49	20.9%	485	28.6%	0.014*
Prenatal Care	367	95.6%	2388	92.7%	0.04*
Pregnancy-induced Hypertension [/]	192	50.4%	329	12.8%	<0.001*
Insulin-dependent diabetes mellitus	19	5%	97	3.8%	0.25
Antenatal Corticosteroids	311	81.2%	1953	76.4%	0.04*
Complete Course	188	61%	1194	62%	0.76
C-section	285	74%	1436	55.6%	<0.001*
Infant					
Gestational Age (week) ⁺	25	23–26	25	23–26	0.65
Multiple Birth	76	19.7%	615	23.5%	0.08
Birth Weight (grams)	524	76	761	149	<0.001*
Birth Length (cm)	29.5	2.3	32.5	2.4	<0.001*
Head Circumference (cm)	21.1	1.2	22.9	1.7	<0.001*
Male Gender	201	52.2%	1381	53.4	0.66
5 min. Apgar Score < 5	121	32%	642	25.2%	0.005*

[#] 1,166 missing data on education.⁺ Values are median (range).

* P-value less than 0.05 is considered significant.

[/] Systolic pressure 140 mmHg or a diastolic pressure 90 mmHg on two occasions 2 to 24 hours apart.

Table 2

Comparison of Secondary Outcomes between SGA and Non-SGA Group

	SGA n = 385		Non-SGA n = 2586		P value
	Mean/N	SD/%	Mean/N	SD/%	
RDS ¹	315	81.8%	2301	89%	<0.001*
Received Surfactant	310	80.5%	2196	84.9%	0.03*
BPD ² (Traditional)	145	37.7%	928	35.9%	0.50
Late-onset Sepsis/Meningitis ³	151	39.2%	943	36.5%	0.30
Necrotizing enterocolitis ⁴ Stage II or >	38	9.9%	304	11.8%	0.28
Surgical patent ductus arteriosus	44	11.4%	401	15.5%	0.04*
Retinopathy of prematurity Stage III or >	52	13.5%	410	15.9%	0.24
Grade III/IV ICH ⁵	61	15.8%	596	23.1%	0.002*
Cystic periventricular leukomalacia	12	3.1%	137	5.3%	0.07
Postnatal Steroid Use	58	15.1%	279	10.8%	0.014*
Duration of Ventilation (Days)	32.4	29.2	25.9	26	<0.001*
Duration of total parenteral nutrition (Days)	32.3	23.3	30.8	23.3	0.54
Length of Stay ⁷ (Days)	71	69	78	60	<0.001*
Mortality	215	55.8%	944	36.5%	<0.001*
Mortality (early deaths excluded) ⁸	145	46%	679	29.3%	<0.001*
Age of Death, days (median/range)	6	1–309	5	1–327	0.69
	n = 179		n = 1454		P value
Weight Velocity to 36 weeks PMA (g/day)	14.5	4.3	17.4	4.7	<0.001*
Growth Failure at 36 weeks PMA	175	97.8%	1115	76.6%	<0.001*
Head Circumference < 10 th Percentile	141	87%	584	42%	<0.001*

PMA – postmenstrual age

* P-value less than 0.05 is considered significant

¹ Based on clinical features and requirement of oxygen/positive pressure support > 6 hrs. in the first 24 hrs. of life.² Oxygen use at 36 weeks postmenstrual age.

- ³Based on culture proven blood and cerebrospinal fluid infection.
- ⁴Defined by Bell staging.
- ⁵Presence of intraventricular or intraparenchymal hemorrhage on head ultrasound.
- ⁶Based on cranial ultrasound findings at 28 days or 36 weeks PMA.
- ⁷Calculated as the number of days between birth and the final known status date. This also includes the time spent at another hospital or chronic care facility.
- ⁸Early death - defined as death 12 hours of age.

Table 3

Comparison of Growth and Neurodevelopmental Outcomes at 18–22 Months Follow-up

	SGA n = 150		Non-SGA n = 1342		P value
	N	%	N	%	
Weight-for-age < 10 th Percentile	90	60%	501	37.4	<0.001 *
Length-for-age < 10 th Percentile	60	40.5%	292	21.9%	<0.001 *
Head Circumference < 10 th Percentile	66	44.9%	292	21.9%	<0.001 *
Growth Failure [#]	102	68%	554	41.3%	<0.001 *
BSID III Cognitive Score <70	18	12.6%	116	8.8%	0.14
BSID III Cognitive Score < 80	38	26.6%	243	18.5%	0.02 *
Language Composite Score <70	37	26.1%	229	17.8%	0.02 *
Moderate or Severe Cerebral Palsy	57	38%	302	22.5%	<0.001 *
Hearing Loss ± Amplification	4	2.7%	36	2.7%	0.99
Blindness (<20/200 Vision B/L)	3	2%	5	0.4%	0.04 *

* P-value less than 0.05 is considered significant

[#] Growth failure - defined as weight and length-for-age <10th percentile.

Table 4

Model Estimated Effects of SGA on Primary Outcome

	Odds Ratio (OR)	95% CI	P value
Death or NDI	3.91	2.91–5.25	<0.001
Death or NDI (early deaths excluded) ^I	3.63	2.68–4.92	<0.001
BSID III Cognitive Score < 70	2.08	1.12–3.85	0.018
BSID III Cognitive Score < 80	2.38	1.49–3.81	<0.001
Moderate or Severe CP	2.55	1.69–3.86	<0.001
Hearing Loss ± Amplification	1.38	0.44–4.36	0.58
Blindness (<20/200 Vision B/L)	10.9	2.15–55.5	0.003

Covariates: center as a random-effect variable, male sex, multiple birth, gestational age, Antenatal corticosteroid, hypertension & maternal education

^I Early death - defined as death < 12 hours of age.