Morbidity and Mortality in Small for Gestational Age Infants at 22 to 29 Weeks' Gestation

Nansi S. Boghossian, PhD, MPH,[a] Marco Geraci, PhD,[a] Erika M. Edwards, PhD, MPH,[b,c,d] Jeffrey D. Horbar, MD[b,c]

abstract

OBJECTIVES: To identify the relative risks of mortality and morbidities for small for gestational age (SGA) infants in comparison with non-SGA infants born at 22 to 29 weeks' gestation.

METHODS: Data were collected (2006–2014) on 156 587 infants from 852 US centers participating in the Vermont Oxford Network. We defined SGA as sex-specific birth weight <10th centile for gestational age (GA) in days. Binomial generalized additive models with a thin plate spline term on GA by SGA were used to calculate the adjusted relative risks and 95% confidence intervals for outcomes by GA.

RESULTS: Compared with non-SGA infants, the risk of patent ductus arteriosus decreased for SGA infants in early GA and then increased in later GA. SGA infants were also at increased risks of mortality, respiratory distress syndrome, necrotizing enterocolitis, late-onset sepsis, severe retinopathy of prematurity, and chronic lung disease. These risks of adverse outcomes, however, were not homogeneous across the GA range. Early-onset sepsis was not different between the 2 groups for the majority of GAs, although severe intraventricular hemorrhage was decreased among SGA infants for only gestational week 24 through week 25.

CONCLUSIONS: SGA was associated with additional risks to mortality and morbidities, but the risks differed across the GA range.

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Dr Boghossian participated in the conception and design of the study, including the analysis plan and in the interpretation of the data, wrote all drafts of the manuscript, and helped to revise it critically for important intellectual content; Dr Geraci participated in designing the analysis plan, was responsible for the data management and data analysis, participated in the interpretation of the data, contributed to writing sections of the manuscript, and helped to revise the manuscript critically for important intellectual content; Dr Edwards participated in the conception of the study and the interpretation of the data and revised the manuscript critically for important intellectual content; Dr Horbar participated in the conception of the study, is the Chief Executive and Scientific Officer of the Vermont Oxford Network (from which the data were drawn), participated in the interpretation of the data, and helped to revise the manuscript critically for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Small for gestational age (SGA) infants are known to be at increased risk of mortality and several morbidities. Previous studies have mainly examined the relative risk of outcomes among SGA versus non-SGA infants, assuming homogeneity across the gestational age range.

WHAT THIS STUDY ADDS: SGA infants had increased risks for mortality, respiratory distress syndrome, necrotizing enterocolitis, late-onset sepsis, severe retinopathy of prematurity, and chronic lung disease and a decreased risk for severe intraventricular hemorrhage, but these risks differed across the gestational age range.

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Intrauterine growth restriction, often defined as small for gestational age (SGA), is known to increase the risk of mortality and morbidities among preterm infants.[1] Previous studies have defined SGA as sex-specific birth weight (BW) <10th centile for gestational age (GA) in weeks rounding down GA to the nearest preceding week[2] and have examined the relative risk (RR) of outcomes among SGA versus non-SGA infants assuming homogeneity across GAs.[3,4] An increase in the risk of adverse outcomes for certain GAs can trigger heightened awareness among care providers who use SGA to identify infants for secondary and tertiary prevention of mortality and morbidities.

We recently published sex-specific BW and head circumference (HC) for GA charts in days using data from the Vermont Oxford Network (VON) on >156 000 infants born at or between 22 to 29 and six-sevenths weeks' gestation.[5] In this study, we define SGA using these charts and examine the risk of mortality and morbidities before initial discharge among SGA versus non-SGA infants across GA.

METHODS

Study Population

Prospectively collected data from 852 NICUs located in the United States or Puerto Rico and participating in the VON Very Low Birth Weight Database (January 1, 2006–December 31, 2014) were analyzed. Included infants had a GA between 22 weeks, 0 days and 29 weeks, 6 days. We restricted our study sample to inborn singleton infants without congenital malformations.[5] The University of Vermont's committee for human research approved the VON's deidentified research repository.

Study Variables

GA in weeks and days was determined by 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 SGA if their BW was below the estimated 10th centile of the corresponding sex-specific BW distribution conditional on the number of gestational days. Estimated centiles were obtained from sex-specific charts, which we have obtained after revising previously published charts.[5] Additional details are provided in supplementary material (Supplemental Figs 5 and 6, Supplemental Table 2). An indicator for postnatal life-support was defined if infants 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.

Outcomes

Mortality was defined as death before hospital discharge. Infants transferred from the reporting hospital to another hospital were tracked for survival status until ultimate disposition or the infant's first birthday. 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 ≥1 instance of (1) left to right or bidirectional ductal shunt on Doppler echo or (2) systolic or continuous murmur and as ≥2 of the following: (1) hyperdynamic precordium, (2) bounding pulses, (3) wide pulse pressure, or (4) pulmonary vascular congestion or cardiomegaly (or both). Necrotizing enterocolitis (NEC) was diagnosed at surgery or postmortem or required ≥1 clinical sign (eg, bilious gastric aspirate, abdominal distension, or occult blood in stool) and ≥1 radiographic finding (eg, pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum).[6] NEC and gastrointestinal 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 by using Papile's classification within 28 days of birth.[7] Severe retinopathy of prematurity (sROP) was defined as stages 3 to 5 on the basis of a retinal examination before hospital discharge.[8] Chronic lung disease (CLD) was defined as continuous use of supplemental oxygen at 36 weeks' postmenstrual age or on oxygen at discharge at 34 to 35 weeks if transferred or discharged before 36 weeks.[6]

Statistical Analysis

We calculated summary statistics of maternal and neonatal characteristics for SGA and non-SGA infants. We also examined the proportion of infants receiving postnatal life-support according to SGA status and gestational days. The estimates and 95% confidence intervals (CIs) were

calculated by using a normal generalized additive model (GAM) with a thin plate spline term on GA by SGA status.[9] Estimates were constrained 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 the following:

1. mortality and morbidity rates before initial discharge among SGA and non-SGA infants by gestational days;
2. unadjusted RRs and 95% CIs for mortality and morbidities among SGA and non-SGA infants by gestational days; and
3. adjusted RRs and 95% CIs for mortality and morbidities among SGA and non-SGA infants by gestational days.

Mortality and morbidity rates (1), unadjusted RRs (2), and adjusted RRs (3) were estimated via normal, Poisson, and binomial GAMs with thin plate spline terms on GA by SGA status, respectively. Adjustments were made for maternal ethnicity and/or race (African American, Hispanic, white, Asian American, other), prenatal care (yes or no), antenatal corticosteroids (ANS) (yes or no), postnatal life-support (yes or no), and newborn sex (male or female). Adjusted RRs for mortality, RDS, and PDA were stratified by ANS status because, for these outcomes only, the interaction between SGA and ANS was significant at the 5% level. We also tested the interaction between SGA and sex, and it was not significant for any of the outcomes. Because early mortality is a competing risk to the examined morbidities, we reran all the adjusted analyses, restricting the data to survivors. Analyses were performed by using R[10] and SAS (version 9.4; SAS Institute, Inc, Cary, NC). GAMs were fitted by using the R package mgcv.[9]

RESULTS

Data were available for 156 587 infants, with 15 581 infants classified as SGA, corresponding to 9.95% of the sample (10.1% at 22 weeks; 9.4% at 23 weeks; 10.2% at 24 weeks; 10.2% at 25 weeks; 9.7% at 26 weeks; 10.0% at 27 weeks; 10.0% at 28 weeks; 9.9% at 29 weeks). Table 1 presents maternal and infant characteristics by SGA status. Mothers of SGA infants were more likely to have had hypertension (66.4% vs 24.2%) and cesarean delivery (91.8% vs 61.7%), but chorioamnionitis (5.1% vs 19.6%) was less likely. This is also presented in Fig 1A, stratified by SGA status and sex with chorioamnionitis higher among non-SGA infants but decreasing as GA increases; and Fig 1B, with hypertension higher among SGA infants and females and increasing as GA increases. As expected, SGA infants had a lower BW, a smaller HC, a lower 5-minutes Apgar score, and more frequent low admission temperatures <36.5°C (62.6% vs 45.5%) (Table 1).

Postnatal life-support was more likely to be delivered to non-SGA than SGA infants at the lower GAs. At 154 days, 29.6% (95% CI: 22.0–38.5) of non-SGA and 11.2% (95% CI: 6.2–19.6) of SGA infants received life-support. This increased to 85.8% (95% CI: 82.9–88.3) and 66.8% (95% CI: 58.3–74.2) at day 161; 98.9% (95% CI: 98.6–99.1) and 95.2% (95% CI: 93.3–96.6) at day 168; and 99.8% (95% CI: 99.8–99.9) and 98.9% (95% CI: 98.5–99.3) at day 175 among non-SGA and SGA infants, respectively. After day 175, life-support became equal (within 1% difference) between the 2 groups. Beyond day 200, SGA infants had more life-support; at 209 days, 94.4% (95% CI: 91.8–96.1) of non-SGA and 98.1% (95% CI: 96.4–99.0) of SGA infants received life-support (Fig 2).

Mortality and morbidity rates among SGA and non-SGA infants are reported in Supplemental Table 3. Figure 3 provides these rates by GA. Supplemental Figure 7 shows the unadjusted RRs and 95% CIs of outcomes comparing SGA to non-SGA infants. For the majority of GAs, SGA infants were at a higher risk of mortality, RDS, PDA, NEC, LOS, sROP, and CLD. These risks, however, were not homogeneous across the GAs. The risks of EOS and sIVH did not differ between the 2 groups for the majority of GAs.

Figure 4 shows the adjusted RRs and 95% CIs for mortality and morbidities comparing SGA to non-SGA infants. For 3 outcomes including mortality, RDS, and PDA, the analyses are stratified by ANS. Below we summarize the findings for the outcomes. There were no meaningful changes in the results after restricting the data to survivors (Supplemental Fig 8).

Mortality

Among infants who did not receive ANS, the risk of mortality among SGA infants was higher starting at week 24 (RR: 1.13; 95% CI: 1.02–1.25) and increased until week 29 (RR: 2.40; 95% CI: 1.36–4.23). Among infants receiving ANS, the risk of mortality among SGA infants was higher starting at week 23 (RR: 1.10; 95% CI: 1.02–1.19) and increased until week 29 (RR: 2.87; 95% CI: 2.11–3.90).

RDS

Among infants who had no ANS, RDS risk among SGA infants did not differ from non-SGA infants. Among infants receiving ANS, however, RDS risk was higher among SGA

TABLE 1 Maternal and Infant Characteristics by SGA Status

	22 wk 154–160 d		23 wk 161–167 d		24 wk 168–174 d		25 wk 175–181 d		22–29 wk 154–209 d	
	SGA *N* = 242	Non-SGA *N* = 2153	SGA *N* = 866	Non-SGA *N* = 8361	SGA *N* = 1760	Non-SGA *N* = 15 464	SGA *N* = 2022	Non-SGA *N* = 17 760	SGA *N* =15 581	Non-SGA *N* = 141 006
Maternal characteristics										
Race										
African American	112/241 (46.5)	874/2138 (40.9)	385/864 (44.6)	3347/8336 (40.2)	734/1759 (41.7)	5805/15 434 (37.6)	784/2021 (38.8)	6397/17 683 (36.1)	5714/15 553 (36.7)	47 172/140 670 (33.5)
Hispanic	45/241 (18.7)	505/2138 (23.6)	185/86 (21.4)	1800/8336 (21.6)	255/1759 (14.5)	3170/15 434 (20.5)	285/2021 (14.1)	3584/17 683 (20.2)	2409/15 553 (15.5)	28 542/140 670 (20.3)
White	70/241 (29.1)	628/2138 (29.4)	270/864 (31.3)	2764/8336 (33.2)	696/1759 (39.6)	5600/15 434 (36.3)	847/2021 (41.9)	6701/17 683 (37.8)	6488/15 553 (41.7)	56 468/140 670 (40.1)
Asian American	10/241 (4.2)	92/2138 (4.3)	15/864 (1.7)	272/8336 (3.3)	50/1759 (2.8)	560/15 434 (3.6)	62/2021 (3.1)	655/17 683 (3.7)	605/15 553 (3.9)	5458/140 670 (3.9)
Other	4/241 (1.7)	39/2138 (1.8)	9/864 (1.0)	153/8336 (1.8)	24/1759 (1.4)	299/15 434 (1.9)	43/2021 (2.1)	388/17 683 (2.2)	337/15 553 (2.2)	3030/140 670 (2.2)
Prenatal care	223/241 (92.5)	1937/2134 (90.8)	817/864 (94.6)	7751/8329 (93.1)	1717/1754 (97.9)	14 494/15 420 (94.0)	1981/2018 (98.2)	16 745/17 695 (94.6)	15 239/15 559 (97.9)	133 594/140 611 (95.0)
Hypertension[a]	28/180 (15.6)	113/1708 (6.6)	289/691 (41.8)	564/6623 (8.5)	958/1425 (67.2)	1563/12 229 (12.8)	1160/1617 (71.7)	2553/13 954 (18.3)	8296/12 503 (66.4)	26 931/111 330 (24.2)
Chorioamnionitis	42/179 (23.5)	502/1703 (29.5)	119/689 (17.3)	1829/6608 (27.7)	141/1424 (9.9)	3307/12 216 (27.1)	82/1616 (5.1)	3258/13 928 (23.4)	635/12 496 (5.1)	21 765/111 161 (19.6)
Hypertension and chorioamnionitis	3/179 (1.7)	28/1698 (1.7)	16/688 (2.3)	129/6598 (2.0)	37/1421 (2.6)	240/12 201 (2.0)	23/1615 (1.4)	255/13 918 (1.8)	189/12 487 (1.5)	1772/111 061 (1.6)
ANS[b]	43/237 (18.1)	518/2141 (24.2)	572/865 (66.1)	5544/8333 (66.5)	1530/1757 (87.1)	12 802/15 427 (83.0)	1790/2013 (88.9)	15 040/17 729 (84.8)	13 481/15 542 (86.7)	11 7039/14 0729 (83.2)
Cesarean delivery	50 (20.7)	310/2152 (14.4)	512 (59.1)	3476/8360 (41.6)	1533 (87.1)	9411/15 462 (60.9)	1907 (94.3)	11 354 (63.9)	14 308/15 580 (91.8)	87 054/140 996 (61.7)
Infant characteristics										
Boy	129 (53.3)	1147 (53.3)	456 (52.7)	4351 (52.0)	906 (51.5)	8116 (52.5)	1090 (53.9)	9353 (52.7)	8228 (52.8)	74 551 (52.9)
Birth wt (g)	394 (38)	521 (70)	430 (47)	599 (77)	450 (56)	680 (91)	481 (64)	776 (112)	604 (155)	974 (274)
HC (cm)	19.2 (1.3)	20.2 (1.5)	19.7 (1.4)	21.0 (1.4)	20.2 (1.4)	21.9 (1.3)	20.8 (1.3)	22.9 (1.3)	22.3 (2.1)	24.5 (2.4)
Apgar at 5 min ≤3	170/213 (79.8)	1264/2003 (63.1)	319/832 (38.3)	2330/8183 (28.5)	368/1729 (21.3)	2343/15 304 (15.3)	278/1999 (13.9)	1800/17 651 (10.2)	1721/15 422 (11.2)	11 707/139 982 (8.4)
Postnatal life-support[c]	76 (31.4)	1188 (55.2)	753 (87.0)	7917 (94.7)	1720 (97.7)	15 394 (99.6)	2001 (99.0)	17 735 (99.9)	15 174/15 581 (97.4)	137 903/141 006 (97.8)
Admission temperature[d]										
36.5–37.5°C	9/59 (15.3)	219/1002 (21.9)	128/657 (19.5)	2186/7265 (30.1)	417/1608 (25.9)	5564/14 765 (37.7)	575/1908 (30.1)	7702/17 204 (44.8)	5092/14 615 (34.8)	65 344/135 522 (48.2)
<36.5°C	49/59 (83.1)	749/1002 (74.8)	515/657 (78.4)	4789/7265 (65.9)	1151/1608 (71.6)	8405/14 765 (56.9)	1279/1908 (67.0)	8372/17 204 (48.7)	9141/14 615 (62.6)	61 622/135 522 (45.5)
>37.5°C	1/59 (1.7)	34/1002 (3.4)	14/657 (2.1)	290/7265 (4.0)	40/1608 (2.5)	796/14 765 (5.4)	54/1908 (2.8)	1130/17 204 (6.6)	382/14 615 (2.6)	8556/135 522 (6.3)
Total length of stay (d) median[e] (IQR)	1 (1–2)	1 (1–21)	10 (2–118)	94 (5–128)	93 (7–135)	103 (52–126)	104 (16–134)	95 (77–114)	80 (50–113)	69 (50–95)

Numbers are *n* (%) unless otherwise indicated. Reported weeks are rounded down to the largest previous week. Chorioamnionitis variable was added in 2008. IQR, interquartile range.

[a] Maternal hypertension is defined as chronic or pregnancy-induced, with or without edema and proteinuria, or as maternal blood pressure >140 systolic or 90 diastolic before or during the present pregnancy.

[b] Exposure to ANS is defined as steroids administered IM or IV to the mother during pregnancy at any time before delivery.

[c] Postnatal life-support includes 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.

[d] Infant's body temperature was measured by taking a rectal, esophageal, tympanic, or axillary temperature and was recorded within the first hour after admission to the NICU.

[e] Data are missing for length of stay on 270 SGA infants and 1276 non-SGA infants.

infants starting at approximately gestational week (GW) 25 (RR: 1.18; 95% CI: 1.08–1.30) and increased until GW 27 (RR: 1.59; 95% CI: 1.43–1.78) but then decreased through week 29 (RR: 1.15; 95% CI: 1.02–1.29).

PDA

Among infants who had no ANS, PDA risk was significantly reduced among SGA infants for only GWs 23 through 24 (RR: ∼0.59; 95% CI: ∼0.35–0.87). Among infants receiving ANS, however, PDA risk was significantly reduced among SGA infants in the earlier gestational period between 23 and 24 weeks (RR: 0.73–0.83; 95% CI: 0.56–0.98) and then increased between 26 and 29 weeks (RR: 1.19–1.46; 95% CI: 1.05–1.83).

NEC

NEC risk was significantly higher among SGA infants starting at GW 27 (RR: 1.44; 95% CI: 1.10–1.88) and increasing to GW 29 (RR: 1.85; 95% CI: 1.22–2.81).

EOS

Although the main effect estimates were decreased among SGA infants for the majority of GWs, few reached statistical significance.

LOS

LOS risk was higher among SGA infants starting at GW 26 (RR: 1.32; 95% CI: 1.05–1.66) and increasing to week 29 (RR: 1.73; 95% CI: 1.13–2.66).

sIVH

The risk of sIVH was lower among SGA infants for only week 24 through 25 (RR: 0.63–0.72; 95% CI: 0.41–0.99).

sROP

The risk of sROP was increased among SGA infants starting at GW 24 (RR: 1.53; 95% CI: 1.21–1.95) through 28 (RR: 4.81; 95% CI: 3.39–6.84) and then decreasing through week 29 (RR: 3.35; 95% CI: 1.41–7.98).

CLD

CLD risk was increased among SGA infants starting at GW 23 (RR: 1.84; 95% CI: 1.30–2.60) through week 27 (RR: 3.56; 95% CI: 3.04–4.18) and then decreasing through week 29 (RR: 2.82; 95% CI: 2.29–3.49).

DISCUSSION

We used the new BW for GA charts for infants born 22 to 29 6/7 weeks' gestation to define SGA and examine associations with outcomes on >156 000 infants. We show that compared with non-SGA infants, SGA infants were at increased risks of mortality, RDS, NEC, LOS, sROP, and CLD. These risks of outcomes, however, were not homogeneous across the GA range. For PDA, the risk was decreased among SGA infants in early GA and then increased in later GA. EOS risk was not different between the 2 groups for the majority of GAs, whereas sIVH risk decreased among SGA infants between weeks 24 and 25.

Being born SGA before 166 gestational days carried a disadvantage of ∼3 gestational days when comparing the life-support rates with non-SGA infants; ie, a 165-day (89.1%; 95% CI: 85.1–92.1) SGA infant received a similar life-support rate as a 162-day (90.0%; 95% CI: 87.8–91.8) non-SGA infant. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development has reported that among infants <24 weeks' gestation, more SGA infants received comfort care (29% vs 18%).[4] At early GAs, it seems that not only GA[11,12] but also growth restriction can impact perceptions about impairment risk and subsequent life-support provision. This lower life-support rate should be considered when reporting on risks of outcomes among SGA infants. The higher life-support rate beyond day 200 among SGA infants reflects their overall poorer health status and their need for more treatment.

That the risk of mortality and morbidities among SGA vs non-SGA infants is differential according to GA is interesting but hard to explain. In the early GAs, before ∼week 24, SGA infants do not appear to have increased risk for the majority of morbidities. Although sample size is a potential reason for this given the wide CIs before week 23, it does not explain the null findings between weeks 23 and 24. It might be that at these early GAs, immaturity predominates the growth restriction effect, or that the higher early mortality of SGA infants competes with their risk of developing these morbidities. Yet restricting the analyses to survivors only did not change our findings. For later GAs, we speculate that the underlying maternal conditions that resulted in the impaired fetal growth and subsequent preterm birth (PTB) might have contributed to a differential risk of mortality and morbidities across the GAs.

On the basis of our data, maternal hypertension, an indicator for iatrogenic delivery, seems to be more prevalent among SGA infants (66% vs 24%), whereas chorioamnionitis, an indicator for preterm premature rupture of membranes or preterm labor, is more prevalent among non-SGA infants (20% vs 5%). Interestingly, maternal hypertension rate among SGA infants increased across GA (15.6% at 22 weeks and 67.5% at 29 weeks), whereas chorioamnionitis rate decreased

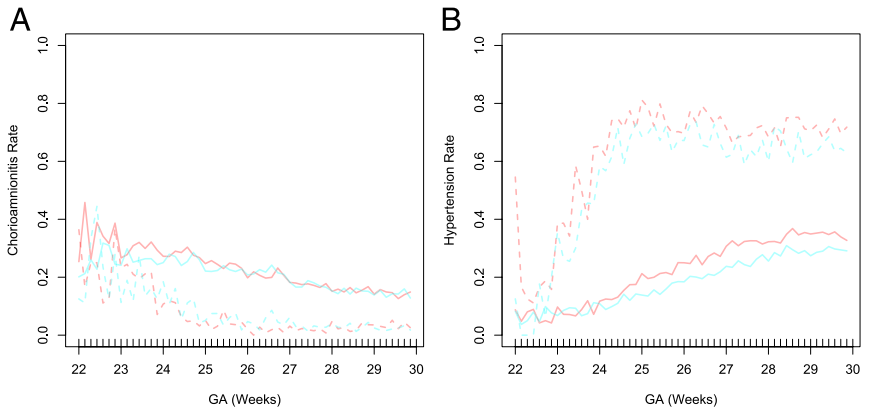

FIGURE 1

A, Chorioamnionitis rate. B, Hypertension rate among SGA and non-SGA infants by sex and GA. The dashed line represents SGA infants and the solid line represents non-SGA infants; blue represents boys and pink represents girls.

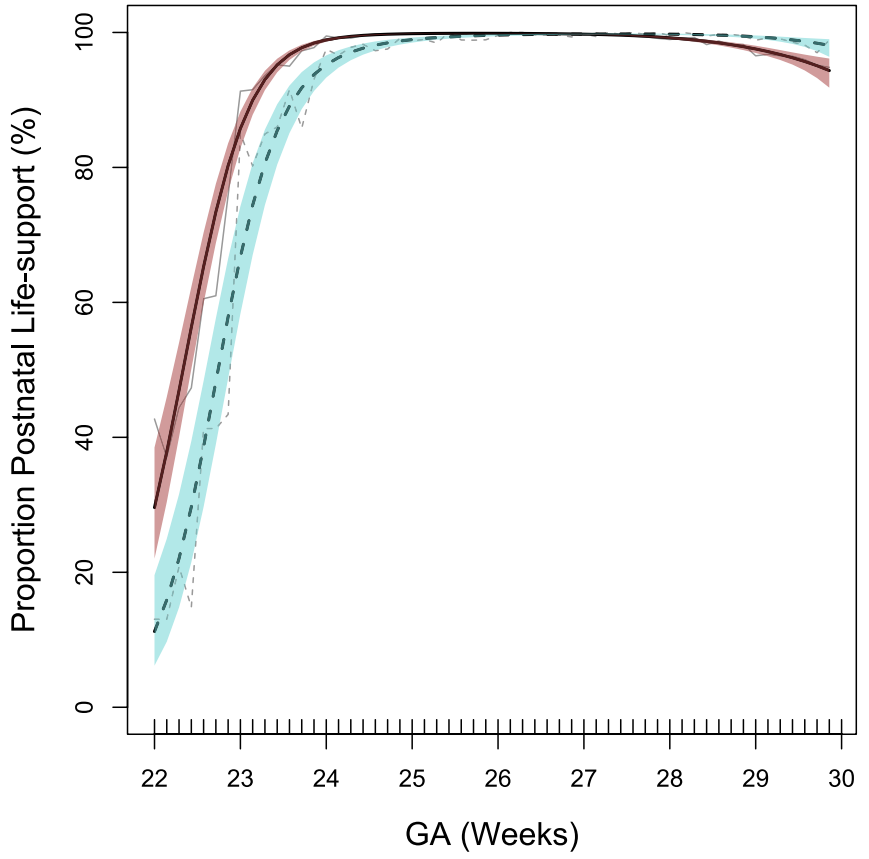

FIGURE 2

Postnatal life-support among SGA and non-SGA infants by GA. The dashed line represents SGA infants and the solid line represents non-SGA infants; borders represent 95% CIs.

(23.5% at 22 weeks and 2.8% at 29 weeks). Among non-SGA infants, hypertension rate also increased across GA (6.6% at 22 weeks to 31.6% at 29 weeks) and chorioamnionitis rate decreased (29.5% at 22 weeks to 14.3% at 29 weeks), albeit on a smaller scale. Previous studies have noted that the chorioamnionitis rate and severity are higher the earlier the PTB ensues.[13,14] The higher observed maternal hypertension rate among female rather than male infants has also been reported.[15–17] Pregnancies carrying male infants had a higher incidence of very PTB after spontaneous labor, whereas female infants had a greater susceptibility to indicated PTB associated with hypertension.[16,17] As such, different causes of PTB might operate at different GAs and might differ by sex.

Knowing the maternal conditions that resulted in the PTB is imperative to understanding the increased risk of morbidities among SGA infants. Although not directly examined, few studies have revealed that certain neonatal morbidities among preterm infants might have an in utero component. A study among 23 to 30 GW infants (n = 3606) reported increased mortality, bronchopulmonary dysplasia (BPD), and sROP among infants born to women with hypertensive disorders compared to those born to women with chorioamnionitis[18]; however, whereas EOS, sIVH, and surgical NEC or gastrointestinal perforation were decreased among infants born to women with hypertension compared to infants born to women with chorioamnionitis.[18] The lack of association and even protective effect of SGA at certain GAs with EOS in our study might reflect the higher chorioamnionitis rate among non-SGA infants. A study in which infants born 22 to 27 weeks' gestation were examined showed significantly lower infant survival when the PTB onset was preterm premature rupture of membranes compared with the other 2 groups of either preterm labor or iatrogenic delivery, although major morbidity (defined as any of sIVH, periventricular leukomalacia, sROP, BPD, or NEC) did not differ between these 3 examined groups.[19] In another study, NEC, BPD, and ROP were related to iatrogenic rather

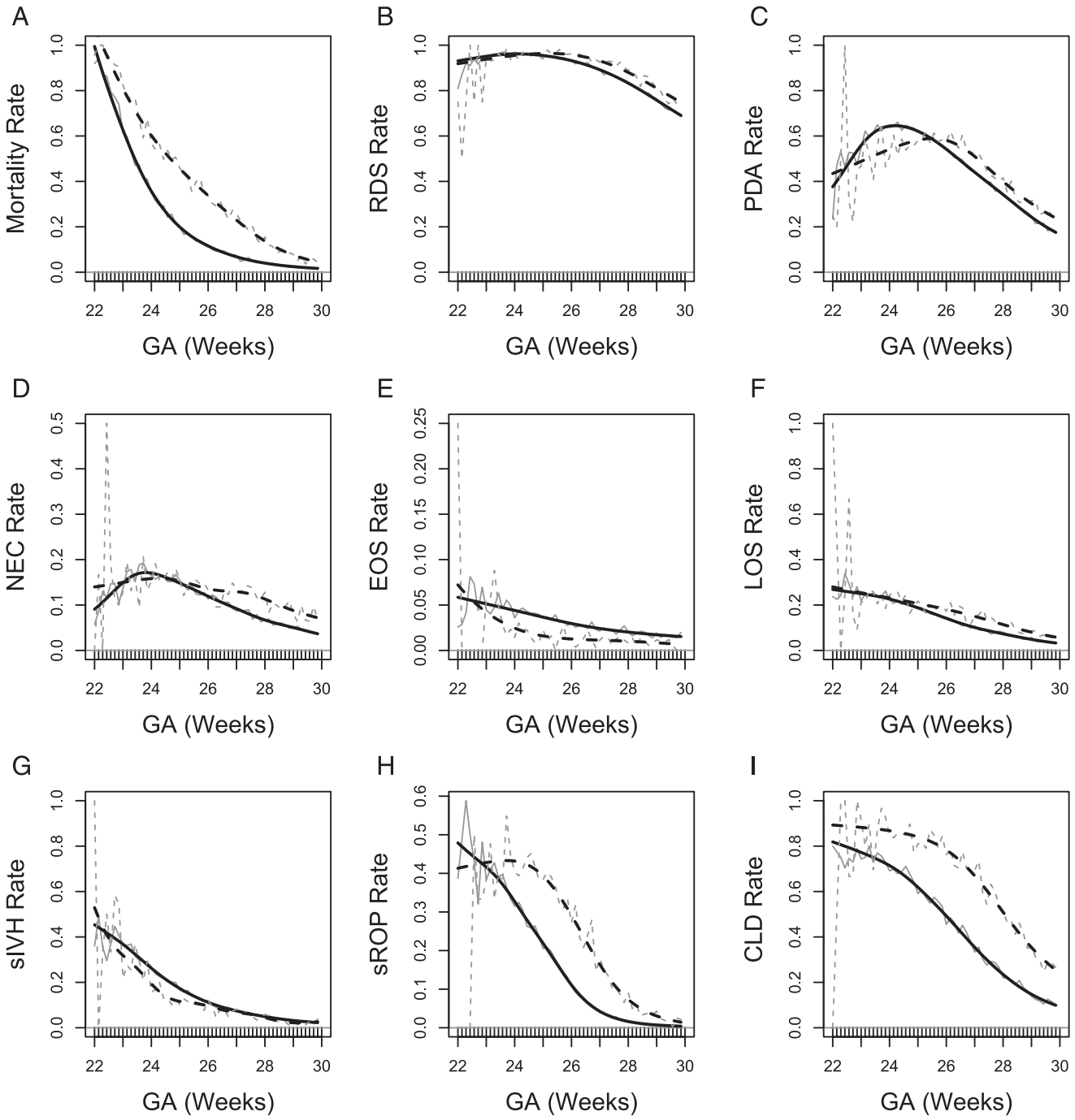

FIGURE 3

Rates of outcomes among SGA and non-SGA infants by GA. A, Mortality rate. B, RDS rate. C, PDA rate. D, NEC rate. E, EOS rate. F, LOS rate. G, sIVH rate. H, sROP rate. I, CLD rate. The dashed line represents SGA infants and the solid line represents non-SGA infants. Note that rates for different outcomes are plotted on different scales.

than spontaneous onset of PTB.[20] However, 1 study reported that the risk patterns in neonatal outcomes were similar by the cause of PTB.[21]

Researchers examining adverse outcomes among preterm SGA infants have been mainly consistent in reporting increased risk or odds of mortality,[3,4,21–28] NEC,[3,22,24,27,28] ROP,[22,23,28,29] and CLD.[21,22,24–26,29] We similarly show an increased risk for these outcomes. For intraventricular hemorrhage, however, researchers have predominantly reported null results,[21,22,27,28,30] a trend toward a decreased incidence,[29,31] or increased risk[3] in association with SGA. We show a significantly decreased sIVH

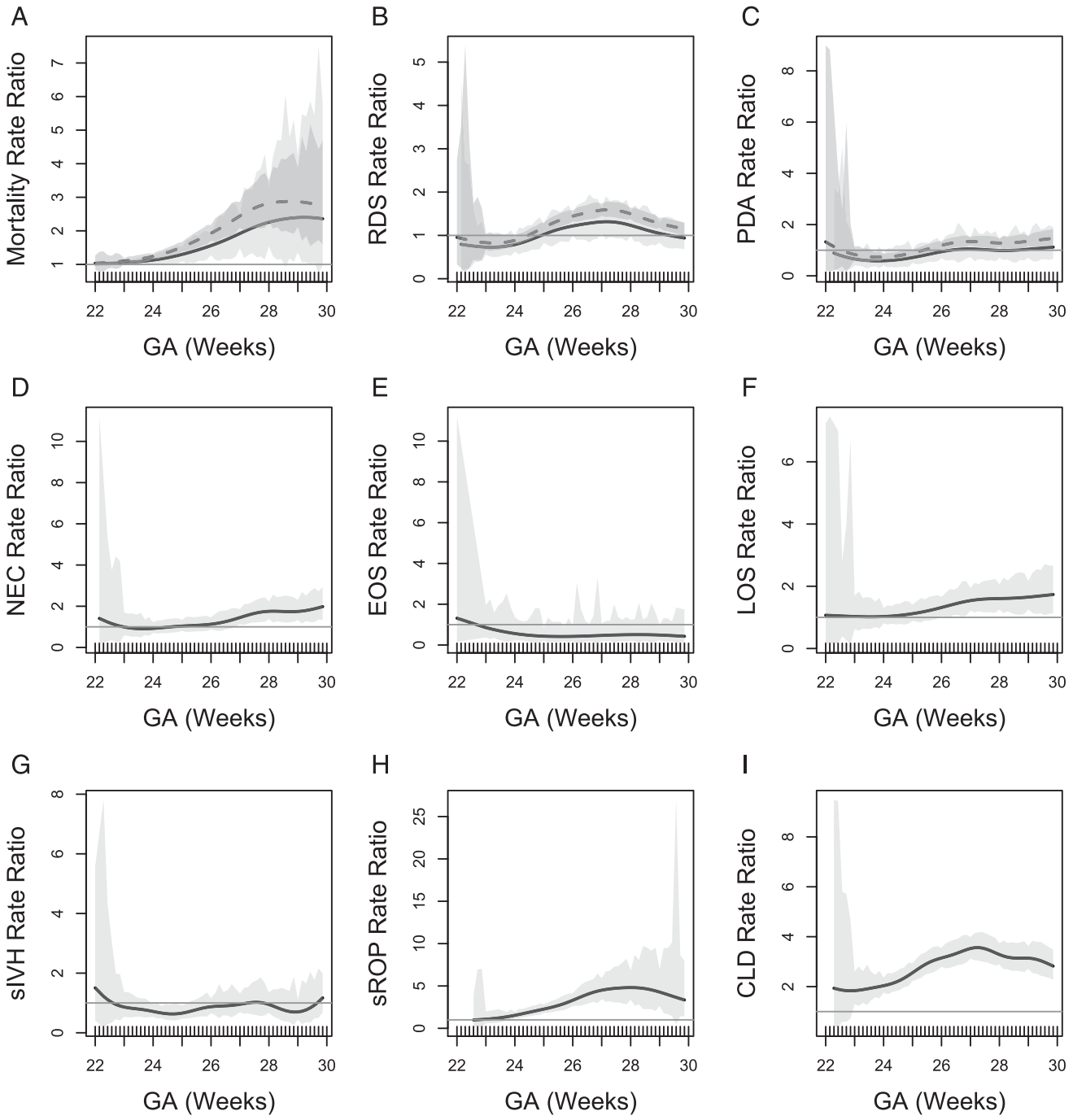

FIGURE 4

Adjusted rate ratios among SGA versus non-SGA infants by GA. A–C, The solid line represents adjusted RR among SGA versus non-SGA infants who had ANS by GA, and the dark gray border represents 95% CI; the dashed line represents adjusted RR among SGA versus non-SGA infants who did not have ANS by GA, and the light gray border represents 95% CI. D–I, The solid line represents adjusted RR among SGA vs non-SGA infants by GA, and the gray border represents 95% CI. Models were adjusted for the following: maternal ethnicity and/or race (African American, Hispanic, white, Asian American, other), prenatal care (yes or no), postnatal life-support (yes or no), and newborn sex (male or female). Models in D–I were also adjusted for ANS. Note that rate ratios for different outcomes are plotted on different scales.

risk among SGA infants for weeks 24 through 25 only. Evidence on RDS risk in association with SGA has been more controversial. Earlier studies have supported the concept of an increased pulmonary maturation among SGA infants.[32–34] More recent studies, however, have reported either an increased RDS risk among SGA infants[3,35] or no difference[28,29] compared with non-SGA infants. We report an increased RDS risk in association with SGA

but only among infants with ANS exposure.

The strengths of our study include a large contemporary sample size representative of the United States 22 to 29 6/7 weeks' gestation newborns, allowing us to examine the risk of outcomes among SGA infants per GW in an unprecedented manner. To do so, we used a flexible approach that allowed us to model nonlinear effects through GAMs uncovering local effects that would otherwise go unnoticed when using standard generalized linear models.[9] Our study has some limitations. Other than hypertension and chorioamnionitis, we had no data on maternal conditions or underlying pathologic mechanisms that resulted in the impaired fetal growth or the PTB. As such, we were unable to explore how growth restriction subtypes can contribute to neonatal outcomes. We were also unable to ascertain the morbidities for some infants who died or were discharged before the outcome could be evaluated. We used GA in number of days, which might have some inaccuracy, but this preserves more information in the data and is better than rounding down.[36] The proportion of infants born at GAs equal to multiples of 7, however, was higher than expected by chance because of rounding during data collection.

CONCLUSIONS

The SGA definition based on the recently developed charts for infants at 22 to 29 6/7 weeks' gestation was associated with additional risks to mortality and morbidities, but the risk of outcomes differed across the GA range, which should be explored in future studies. The observed increased risk of adverse outcomes among SGA infants can be used for perinatal management.

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ABBREVIATIONS

ANS: antenatal corticosteroids
BPD: bronchopulmonary dysplasia
BW: birth weight
CI: confidence interval
CLD: chronic lung disease
EOS: early-onset sepsis
GA: gestational age
GAM: generalized additive model
GAMLSS: generalized additive models for location, scale, and shape
GW: gestational week
HC: head circumference
LOS: late-onset sepsis
NEC: necrotizing enterocolitis
PDA: patent ductus arteriosus
PTB: preterm birth
RDS: respiratory distress syndrome
RR: relative risk
SGA: small for gestational age
sIVH: severe intraventricular hemorrhage
sROP: severe retinopathy of prematurity
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