Title

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ORIGINAL ARTICLE

The smallest of the small: short-term outcomes of profoundly growth restricted and profoundly low birth weight preterm infants

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OBJECTIVE: Survival of preterm and very low birth weight (VLBW) infants has steadily improved. However, the rates of mortality and morbidity among the very smallest infants are poorly characterized.

STUDY DESIGN: Data from the California Perinatal Quality Care Collaborative for the years 2005 to 2012 were used to compare the mortality and morbidity of profoundly low birth weight (ProLBW, birth weight 300 to 500 g) and profoundly small for gestational age (ProSGA, < 1st centile for weight-for-age) infants with very low birth weight (VLBW, birth weight 500 to 1500 g) and appropriate for gestational age (AGA, 5th to 95th centile for weight-for-age) infants, respectively.

RESULT: Data were available for 44 561 neonates of birth weight < 1500 g. Of these, 1824 were ProLBW and 648 were ProSGA. ProLBW and ProSGA differed in their antenatal risk factors from the comparison groups and were less likely to receive antenatal steroids or to be delivered by cesarean section. Only 14% of ProSGA and 21% of ProLBW infants survived to hospital discharge, compared with > 80% of AGA and VLBW infants. The largest increase in mortality in ProSGA and ProLBW infants occurred prior to 12 h of age, and most mortality happened in this time period. Survival of the ProLBW and ProSGA infants was positively associated with higher gestational age, receipt of antenatal steroids, cesarean section delivery and singleton birth.

CONCLUSION: Survival of ProLBW and ProSGA infants is uncommon, and survival without substantial morbidity is rare. Survival is positively associated with receipt of antenatal steroids and cesarean delivery.

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INTRODUCTION

Survival among preterm infants has increased steadily. Media outlets are replete with reports of 'miraculous' survival of extremely small preterm infants, much of which poorly informs the realites of survival and risk of morbidity.[1] Although clear data on outcomes and risk of mortality are required in order to make appropriate shared decisions about the care of these patients, there is relatively little population-based data on the mortality and morbidity associated with being born extremely small or extremely small for gestational age (SGA). The data that are available suggest that mortality rates are very high and that the majority of the deaths in this group occurred in the delivery room.[2]

In California, the California Perinatal Quality Care Collaborative (CPQCC) is a group of 132 public and private member hospitals, including all the California Children's Services-approved Intermediate, Community and Regional level neonatal intensive care units (NICU). The CPQCC collects data on infants born weighing < 1500 g at birth from its member institutions using standardized reporting forms and definitions and receives data for > 90% of such births in California. As such, the CPQCC has proven to be a valuable tool to audit and improve care of preterm babies in California and provides a broad and rich data set to inform medical and parental decision making for these high-risk infants.[3–6]

The current study was a retrospective database review of births < 32 weeks gestation and < 1500 g birth weight reported to the CPQCC between 2005 and 2012. Profoundly SGA (ProSGA, birth weight < 1st centile for age) and profoundly low birth weight (ProLBW, birth weight 300 to 500 g) subjects were identified, and comparisons were made between the ProSGA infants and appropriate for gestational age infants (AGA, 5th to 95th weight centile at birth) and between ProLBW and very low birth weight (VLBW) infants (birth weight 501 to 1500 g).

We hypothesized that survival would be significantly lower in ProLBW and ProSGA infants, even after correction for identifiable risk factors, and that the majority of mortality in these groups would occur early in the hospital course.

METHODS

Database management

Data were extracted from the CPQCC database for the years 2005 to 2012 inclusive. During the study period, member institutions reported data on all infants with birth weight between 400 and 1500 g, or gestational age 22 0/7 weeks to 29 6/7 weeks, using the standardized reporting forms and definitions.

Data were extracted from the database in May 2014 and limited to subjects whose gestational age at birth was 154 days (22 weeks 0 days) to 224 days (32 weeks 0 days), whose birth weight was between 300 g and

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1500 g and who were admitted to the reporting institution on or before day 3 of life.

Definitions

Demographic variables. Birth and discharge weights were converted to age-specific *Z*-scores (s.d. scores) based on the published LMS (lamda, mu, sigma) data[7] for the 1993 Fenton growth reference[8] as described elsewhere.[9] *Z*-scores were only calculated for ages between 22 and 50 weeks gestation.

ProSGA infants were defined as those with a birth weight for gestational age less than the first centile ($Z < -2.326$) and AGA infants as those with a birth weight for age between the 5th and 95th centile (*Z*-score −1.645 to +1.645). ProLBW infants were defined as those with a birth weight between 300 and 500 g and VLBW infants as those with birth weight 501 to 1500 g.

Premature rupture of the membrane (ROM) was defined as ROM before the onset of labor, and prolonged ROM as ROM for >18 h. Data were also collected on whether any antenatal steroids were given prior to delivery, whether group B streptococcal screening was positive and whether there had been an antenatal or obstetric bleed (including an abruption or placenta previa). Maternal diagnoses recorded included hypertensive disorders (including pregnancy induced hypertension), diabetes mellitus, chorioamnionitis and the presence of multiple gestations (twin or greater). Mode of delivery (non-instrumental vaginal, instrumental vaginal or cesarean) and Apgar scores at 1, 5 and 10 min were recorded. Apgar scores were analyzed both for the entire data set and restricted to infants who were admitted alive from Labor and Delivery (L&D).

Outcomes. Mortality rates were calculated at three distinct times:

prior to admission to the NICU from L&D,
before 12 h of age, and
before discharge;

and for the intervals between them:

between birth and admission to the NICU,
between admission from L&D and 12 h,
between 12 h and final discharge home.

Mortality data were examined for each 100 g cohort (300 to 400 g, 401 to 500 g, 501 to 600 g and so on) individually. Within each cohort, mortality at different time periods was expressed as a percentage of all the recorded births and as a percentage of all the recorded deaths.

Neurological outcomes available included the highest documented grade of intraventricular hemorrhage, the presence of periventricular leukomalacia on ultrasound and whether a ventriculoperitoneal shunt had been inserted. Severe intraventricular hemorrhages were defined as those of grade ⩾3.

Gastrointestinal outcomes examined included necrotizing enterocolitis (NEC), NEC requiring surgical intervention, and isolated gastrointestinal perforations.

The highest grade of retinopathy of prematurity was recorded as was the need for surgical treatment or treatment with vascular endothelial growth factor inhibitor. Severe retinopathy of prematurity was defined as stage ⩾3.

Sepsis was classified as early (before 3 days of age) or late (after 3 days of life). Late sepsis was subdivided into episodes with a bacterial or fungal pathogen.

Chronic lung disease was defined as a need for continuous or intermittent oxygen at 36 week-corrected gestational age.

Growth outcomes were assessed using the change in weight *Z*-score between birth and hospital discharge (as a continuous variable) and as the proportion of subjects whose weight *Z*-score fell by >0.67 *Z*-scores (equivalent to a change of 1 centile line on most infant growth charts) or by >1.0 *Z*-nit. Analysis of growth outcomes was restricted to subjects who were discharged home alive.

The use of composite outcomes (for example, death or NEC) was avoided as they can combine outcomes with different etiologies and risk factors. However, data for 'survival without major morbidity' are presented and defined as survival without chronic lung disease, without surgical NEC, without surgery for gastrointestinal perforation, without grade 3 or 4 intraventricular hemorrhage, without periventricular leukomalacia, without ventriculoperitoneal shunt insertion and without surgery or vascular endothelial growth factor inhibitor treatment for retinopathy of prematurity. Early and late sepsis and medical NEC were not part of this diagnosis.

Statistical methods

Two principle comparisons were made: (1) between ProSGA (birth weight < 1st centile for age) and AGA (birth weight 5th to 95th centile for age) infants and (2) between ProLBW (birth weight 300 to 500 g) and VLBW infants (birth weight 501–1500g).

Descriptive statistics for groups are given as mean (95% confidence interval (95% CI)) for continuous variables and as percentage (95% CI) for nominal variables. Nominal variables were compared using likelihood ratio chi-squared test, and continuous variables were compared by analysis of variance.

The odds of specific nominal outcomes between groups were compared using a series of logistic regression models and expressed as an odds ratio (OR) and 95% CI. Unadjusted ORs were calculated (model no. 1) as were ORs adjusted for antenatal factors (gender, use of antenatal steroids, delivery mode (C/section or not) and multiple gestation) and gestational age (model no. 2); for antenatal factors and birth weight (for ProSGA vs AGA infants) or birth weight *Z*-score (for ProLBW vs extremely LBW (VLBW) infants) (model no. 3); and for antenatal factors, gestational age and birth weight (for ProSGA vs AGA infants) or birth weight *Z*-score (for ProLBW vs VLBW infants) (model no. 4).

Within each group (ProSGA, AGA, ProLBW, VLBW and the entire cohort), potential factors affecting the chance of survival to hospital discharge were assessed using logistic regression. Potential explanatory factors were gender, gestational age, birth weight, birth weight *Z*-score, use of antenatal steroids, delivery by cesarean section and multiple gestation. All analyses were conducted using JMP Pro 11.0.0 (SAS Institute, Cary, NC, USA). A *P*-value <0.05 was taken as statistically significant.

RESULTS

Data were available on 44 561 subjects and were relatively uniformly distributed between different birth years (2005 *n* = 5358, 2006 *n* = 6008, 2007 *n* = 6114, 2008 *n* = 5790, 2009 *n* = 5644, 2010 *n* = 5315, 2011 *n* = 5203, 2012 *n* = 5129).

The mortality rate for the entire cohort was 16.4% (95% CI 16.0 to 16.7%). In all, 5.1% of infants (95% CI 4.9 to 5.3%) died in L&D and were not admitted to the NICU, while 6.8% (95% CI 6.5 to 7.0%) died before 12 h of age.

Mortality decreased rapidly with increasing birth weight (Figure 1) and was <50% once birth weight >600 g. Odds of mortality were significantly lower in those receiving antenatal steroids (OR 0.39 (95% CI 0.37 to 0.42), $P < 0.0001$), those delivered by cesarean section (0.76 (95% CI 0.71 to 0.82), $P < 0.0001$) and in those of greater birth weight ($P < 0.0001$), greater gestational age ($P < 0.0001$) and greater birth weight *Z*-score ($P < 0.0001$).

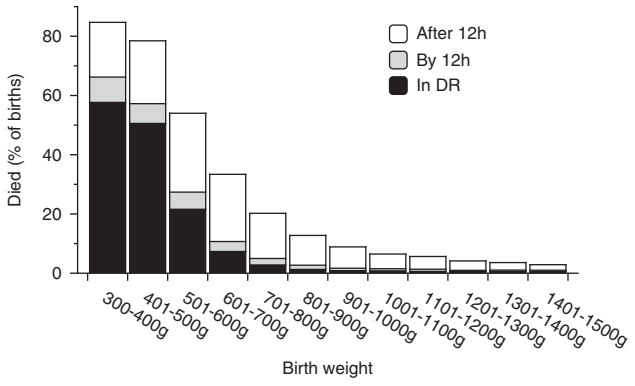

Figure 1. Mortality rates (expressed as a percentage of all births) prior to hospital admission, by 12 h or age and after 12 h of age for different birth weight strata.

In the smallest infants, most mortality occurred before 12 h of age (Figure 2). For infants weighing < 600 g, half of the total mortality occurred prior to 12 h of age, and this decreased to about 25% for infants weighing 1000 g at birth. In larger infants (>1000 g at birth), the relative contribution of early deaths increased as the amount of early deaths reached a plateau but later deaths continued to decrease.

Antenatal factors

ProSGA infants. Data for 648 infants born below the first centile of weight for age were compared with 24 670 infants born between the 5th and the 95th weight for age centile. ProSGA infants weighed less than half the weight of the AGA infants and were born >21 days earlier (Table 1). All the ProSGA infants weighed < 500 g (range 300 to 455 g).

Mothers of ProSGA infants were significantly more likely to be diagnosed with hypertensive disorders and significantly less likely to be diagnosed with diabetes. ProSGA infants were significantly less likely to have prolonged ROM, less likely to be group B streptococci positive and less likely to have fetal distress or be delivered by cesarean section. They were also significantly less likely to receive antenatal corticosteroids (Table 1).

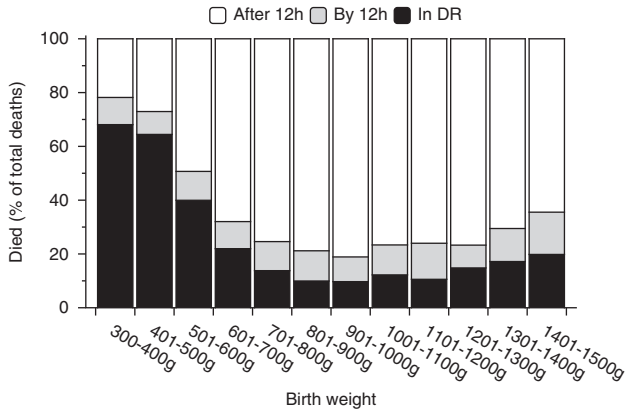

Figure 2. Mortality rates (expressed as a percentage of all deaths) prior to hospital admission, by 12 h or age and after 12 h of age for different birth.

ProLBW infants. Data for 1824 ProLBW infants (birth weight 300 to 500 g) were compared with 42 164 VLBW infants (birth weight 501 to 1500 g). Two hundred and fifty-nine of the ProLBW infants weighed between 300 and 400 g (14.1%), while 1565 (85.9%) weighed between 401 and 500 g at birth. In all, 35% (648) infants were both ProSGA and ProLBW, and 65% were ProLBW but not ProSGA.

ProLBW were much more likely to be SGA than VLBW infants (100% vs 4.4%) and more likely to be born preterm (Table 1). Prolonged ROM was less likely in ProLBW than VLBW, and they were less likely to receive antenatal steroids or to be delivered by cesarean section.

Delivery factors

Apgar scores at 1, 5 and 10 min were significantly lower in the ProSGA and ProLBW infants than in the AGA or VLBW comparison groups (Table 1). The differences were less marked when the analyses were restricted to infants who were admitted alive from L&D and were more similar between groups at 5 and 10 min of age than at 1 min of age.

Neonatal outcomes

ProSGA and ProLBW infants were discharged home at similar, or lower, mean weights than their AGA and VLBW peers. However, their average length of stay was significantly longer, and they were discharged at a significantly older corrected gestational age (Table 2).

Mortality. The unadjusted incidence (Table 2) and odds (Table 3) of mortality were significantly increased in the ProSGA infants compared with the AGA infants and in the ProLBW infants compared with the VLBW infants. The odds of mortality were most

Table 1. Demographic variables for the ProSGA cohort and the comparison AGA cohort and for the ProLBW cohort and the comparison AGA cohort

	Profoundly SGA	*AGA*	P-*value*	*Profoundly LBW*	*VLBW*	P-*value*
Number	648	24 470		1824	42 163	
Male (%)	58.8% (55.0–62.5%)	52.8% (52.2–53.5%)	< 0.0001	45.2% (43.0–47.5%)	52.4% (51.9–53.0%)	< 0.0001
SGA (%)	NA	NA	NA	100% (NA)	4.4% (4.2–4.6%)	< 0.0001
Birth weight (g)	402 (399–404)	866 (864–867)	< 0.0001	NA	NA	NA
Birth weight (*Z*-score)	NA	NA	NA	− 2.27 ((−2.28)-(−2.26))	0.94 (0.93–0.96)	< 0.0001
Gestational age (days)	165.6 (164.6–166.5)	187.7 (187.5–187.8)	< 0.0001	166.1 (165.6–166.7)	194.8 (195.7–195.0)	< 0.0001
Fetal distress (%)	17.3% (14.5–20.4%)	22.7% (22.1–23.2%)	0.0010	18.2% (16.5–20.1%)	21.2% (20.8–21.6%)	0.0030
Chorioamnionitis (%)	7.4% (5.2–10.5%)	9.0% (8.5–9.4%)	0.28	9.0% (7.5–10.8%)	7.7% (7.4–8.0%)	0.13
Antenatal steroids (%)	41.8% (38.0–45.7%)	79.1% (78.6–79.6%)	< 0.0001	43.1% (40.8–45.4)	78.8% (78.3–79.2%)	< 0.0001
Antenatal hypertension (%)	30.9% (27.4–34.7%)	22.9% (22.4–23.5%)	< 0.0001	23.3% (21.4–25.4%)	23.6% (23.2–24.0%)	0.82
Antenatal diabetes (%)	4.1% (2.8–5.9%)	8.0% (7.7–8.4%)	< 0.0001	5.4% (4.4–6.5%)	8.9% (8.6–9.2%)	< 0.0001
Antenatal bleed (%)	15.7% (13.1–18.8%)	20.0% (19.6–20.6%)	0.005	16.0% (14.3–17.8%)	19.2% (18.8–19.6%)	0.001
Preterm ROM (%)	30.0% (26.5–33.7%)	33.6% (33.0–34.2%)	0.06	33.8% (31.6–36.1%)	33.4% (33.0–33.9%)	0.73
Prolonged ROM (%)	10.3% (8.1–12.9%)	16.1% 915.6–16.6%)	< 0.0001	12.5% (11.0–14.1%)	16.3% (16.0–16.7%)	< 0.0001
GBS positive (%)	16.8% (10.9–25.0%)	26.5% (25.5–27.5%)	0.018	22.2% (18.2–27.0%)	26.4% (25.7–27.2%)	0.08
Multiple gestation (%)	27.0% (23.8–30.6%)	24.2% (23.6–24.7%)	0.09	26.3% (24.3–28.4%)	26.4% (26.0–26.8%)	0.91
C/section (%)	44.5% (40.7–48.4%)	71.7% (71.2–72.3%)	< 0.0001	42.4% (40.1–44.6%)	70.9% 70.5–71.4%)	< 0.0001
Apgar—1 min	2.21 (2.07–2.35)	4.88 (4.85–4.91)	< 0.0001	2.41 (2.32–2.50)	5.33 (5.30–5.35)	< 0.0001
Apgar—5 min	2.90 (2.69–3.11)	6.88 (6.85–6.91)	< 0.0001	3.27 (3.14–3.40)	7.15 (7.13–7.18)	< 0.0001
Apgar—10 min	2.67 (2.39–2.94)	6.47 (6.42–6.52)	< 0.0001	3.19 (3.02–3.37)	6.46 (6.42–6.51)	< 0.0001
Apgar—1min[†]	3.21 (2.94–3.47)	4.97 (4.94–5.00)	< 0.0001	3.34 (3.20–3.48)	5.44 (5.42–5.47)	< 0.0001
Apgar—5 min[†]	5.36 (5.05–5.67)	7.03 (7.01–7.06)	< 0.0001	5.45 (5.28–5.61)	7.34 (7.32–7.35)	< 0.0001
Apgar—10 min[†]	5.57 (5.20–5.95)	6.79 (6.72–6.81)	< 0.0001	5.66 (5.45–5.86)	6.83 (6.79–6.86)	< 0.0001

Abbreviations: AGA, appropriate for gestational age; GBS, group B streptococci; LBW, low birth weight; NA, not applicable; ROM, rupture of membranes; SGA, small for gestational age; VLBW, very low birth weight. [†]Analysis limited to infants who were admitted alive from L&D.

Table 2. Outcome data for the ProSGA cohort and the comparison AGA cohort and for the ProLBW cohort and the comparison AGA cohort

	Profoundly SGA	*AGA*	P-*value*	*Profoundly LBW*	*VLBW*	P-*value*
Mortality						
Survived to discharge home, *n* (%)	93 (14.4%)	20 145 (82.3%)	< 0.0001	376 (20.6%)	35 989 (85.4%)	< 0.0001
Discharge characteristics						
Discharge weight	2160.2 (1902.4–2417.9)	2304.9 (2291.4–2318.3)	0.15	2166.2 (2041.9–2290.5)	2314 (2305–2322)	0.0009
Length of stay (days)	101.7 (89.0–114.5)	66.9 (66.3–67.4)	< 0.0001	95.6 (89.7–101.5)	57.5 (57.1–57.9)	< 0.0001
Postmenstrual age at discharge (days)	279.2 (266.2–292.3)	256.5 (256.0–257.00	< 0.0001	271.9 (265.9–277.8)	255.0 (254.7–255.4)	< 0.0001
Growth[a]						
Discharge weight *Z*-score	− 3.08 ((−3.36) – (−2.80))	− 1.42 ((− 1.44) – (− 1.41))	< 0.0001	− 2.70 ((−2.84) – (−2.57))	− 1.28 ((− 1.29) – (− 1.27))	< 0.0001
Discharge weight *Z*-score < 5th centile (%)	88.0% (79.2–93.3%)	38.0% (37.4–38.8%)	< 0.0001	80.7% (76.3–84.5%)	31.5% (31.0–32.0%)	< 0.0001
Discharge weight *Z*-score < 10th centile (%)	98.8% (93.5–99.8%)	55.3% (54.6–56.0%)	< 0.0001	91.4% (88.0–93.9%)	49.6% (49.1–50.1%	< 0.0001
Change in weight *Z*-score birth to discharge	− 0.59 ((−0.86) – (−0.32))	− 1.55 ((− 1.56) – (− 1.53))	0.0007	− 0.50 ((−0.63) – (−0.37))	− 2.47 ((− 2.49) – (− 2.46))	< 0.0001
Fall in weight *Z*-score > 0.67 (%)	39.8% (29.9–50.5%)	74.8% (74.2–75.4%)	< 0.0001	36.5% (31.6–41.7%)	84.7% (84.2–85.0%)	< 0.0001
Fall in weight *Z*-score > 1.00 (%)	33.7% (24.5–44.4%)	66.3% (65.6–67.0%)	< 0.0001	29.9% (25.3–34.9%)	79.7% (79.3–80.0%)	< 0.0001
Mortality						
Died prior to NICU admission (%)	59.3% (55.4–53.0%)	2.8% (2.6–30.5%)	< 0.0001	51.0% (48.7–53.3%)	3.02% (2.86–3.18%)	< 0.0001
Died before 12 h of age (%)	65.1% (61.4–68.7%)	4.5% (4.2–4.8%)	< 0.0001	57.9% (55.6–60.1%)	4.47% (4.27–4.67%)	< 0.0001
Died before discharge home (%)	85.5% (82.6–88.0%)	16.5% (16.1–17.0%)	< 0.0001	79.2% (77.2–81.0%)	13.64% (13.31–13.97%)	< 0.0001
Morbidities						
Early sepsis (< 3 days) (%)	1.15% (0.39–3.32%)	2.13% (1.96–2.32%)	0.2300	1.48% (0.87–2.51%)	1.77% (1.65–1.90%)	0.50
Late bacterial sepsis (> 3 days) (%)	22.3% (17.0–28.8%)	12.8% (12.4–13.3%)	0.0003	23.1% (20.0–26.6%)	9.7% (8.4–10.0%)	< 0.0001
Late fungal sepsis (> 3 days)) (%)	2.66% (1.14–6.07%)	0.95% (0.82–1.08%)	0.0481	1.78% (1.00–3.16%)	0.67% (0.59–0.75%)	0.0055
Late sepsis (> 3 days) (bacterial or fungal) (%)	22.9% (17.4–29.4%)	13.5% (13.0–13.9%)	0.0005	23.9% (20.8–27.5%)	10.2% (9.9–10.5%)	< 0.0001
CLD (%)—O_2 at 36 weeks	71.2% (65.5–76.4%)	49.1% (48.5–49.7%)	< 0.0001	66.1% (63.0–69.2%)	37.3% (36.8–37.8%)	< 0.0001
Severe ROP (%)	42.3% (32.9–52.2%)	12.8% (12.3–13.4%)	< 0.0001	40.0% (34.6–44.6%)	8.6% (8.3–8.9%)	< 0.0001
ROP surgery or VEGF treatment (%)	40.2% (31.0–50.2%)	10.8% (10.3–11.3%)	< 0.0001	33.8% (29.1–38.8%)	7.2% (6.9–7.5%)	< 0.0001
Grade 3 or 4 IVH (%)	19.2% (14.4–25.2%)	13.7% (13.3–14.2%)	0.0308	20.5% (17.7–23.7%)	10.0% (9.7–10.3%)	< 0.0001
PVL (%)	0.49% (0.09–2.72%	3.22% (2.99–3.46%)	0.0063	3.17% (2.10–4.75%)	2.58% (2.42–2.74%)	0.35
NEC (%)	11.0% (7.7–15.3%)	8.2% (7.8–8.5%)	0.12	8.75% (7.07–10.79%)	6.47% (6.23–6.71%)	0.0092
Surgical NEC (%)	5.68% (3.47–9.17%)	3.22% (3.01–3.46%)	0.0435	3.71% (2.65–5.16%)	2.42% (2.28–2.58%)	0.0222
Isolated GI perforation (%)	7.28% (4.71–11.09%)	4.96% (4.67–5.23%)	0.11	5.75% (4.40–7.48%)	3.47% (3.29–3.65%)	0.0008

Abbreviations: AGA, appropriate for gestational age; CLD, chronic lung disease; GI, gastrointestinal; IVH, intraventricular hemorrhage; LBW, low birth weight; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SGA, small for gestational age; VEGF, vascular endothelial growth factor; VLBW, very low birth weight. [a]Among those who survived to discharge.

increased prior to admission to the NICU but remained elevated between admission and 12 h of life and after 12 h of life.

Correcting for obstetric factors had little effect on the odds of death (Table 3). Correcting for differences in gestational age reduced the excess odds of mortality, and correcting for both gestational age and for body size (either birth weight or birth weight Z-score) reduced it further.

However, mortality remained significantly higher in the ProSGA and ProLBW groups even after correcting for obstetric factors, gestational age and birth size (either birth weight or birth weight *Z*-score; Table 3).

At birth weights < 601 g, mortality rates exceeded 50% (Figure 1) and more than half of the mortality occurred before 12 h of age (Figure 2). Above birth weights of 900 to 1000 g, the mortality rate before NICU admission stabilized, but later mortality continued to fall (Figure 1), leading to a greater proportion of deaths occurring early in the hospital course (Figure 2).

Even among the ProLBW infants, mortality was related to birth weight and was significantly higher for infants weighing 300 to 400 g (84.0%, 91% CI 80.0 to 88.0%) than for those weighing 401 to 500 g (78%, 95% CI 76.5 to 77.3%, $P < 0.0001$) at birth.

Growth. ProSGA and ProLBW infants were at significantly increased risk of being discharged home below the 5th or 10th weight for age centile (Tables 2 and 3) than AGA or VLBW infants. These odds were further increased after correcting for antenatal factors. They remained elevated even when accounting for gestational age, body size or both.

When in-hospital growth was expressed by the difference in weight for age *Z*-score at birth and at discharge, the unadjusted incidence and odds of poor growth (a fall in weight *Z*-score of either $\geqslant 0.67$ or $\geqslant 1.0$) was significantly lower in ProSGA and ProLBW infants than in AGA or VLBW. This is presumably due to regression to the mean as random factors are more likely to move extreme outliers closer to the mean, than further away. Once body size variables (birth weight or birth weight *Z*-score) were accounted for, poor growth was significantly more likely in ProSGA and ProLBW infants than in AGA or VLBW.

Neonatal morbidities. Many neonatal morbidities were more common in ProSGA or ProLBW infants than in the AGA or VLBW comparison groups (Table 3). In some cases (for example, later bacterial or fungal sepsis), this effect was lost after correcting for obstetric factors, gestational age and birth weight/birth weight *Z*-score, suggesting that these identifiable factors explained the observed differences in risk. In other instances (for example, periventricular leukomalacia), risk was lower in ProSGA or ProLBW infants than in the AGA or VLBW comparison groups following correcting for obstetric factors, gestational age and birth weight/ birth weight *Z*-score. In other words, the increased risk in ProSGA and ProLBW was less than would have been expected based on these risk factors.

Predictors of survival to discharge home

Survival to discharge home was significantly greater in infants of older gestational age, higher birth weight and higher birth weight *Z*-score. Survival was also greater in infants who received antenatal steroids, those who were delivered by cesarean section and in singletons. The effect of C/section on mortality was limited to before 12 h of age, and the effect of multiple gestation on mortality was limited to deaths prior to 12 h of age (Table 4).

Among ProSGA and ProLBW babies, overall mortality was higher in those receiving antenatal steroids, those delivered by C/section and in singletons and lower in those of higher gestational age. The effect of birth weight (or birth weight *Z*-score) was not significant within the cohorts of ProSGA or ProLBW infants but was significant for the entire cohort. Females had a significantly higher chance of survival in the entire cohort but not in the subsets of ProSGA or ProLBW infants. The beneficial effect of C/section was seen on mortality in L&D and mortality prior to 12 h of age but not in mortality after 12 h of age (Table 4). Conversely, the beneficial effect of singleton delivery on mortality was only seen after 12 h of age and not in mortality in L&D or prior to 12 h of age.

Survival without substantial morbidity

Survival without substantial morbidity increased with increasing birth weight (Figure 3) but did not exceed 50% until birth weight exceeded 1 kg.

DISCUSSION

Infants born below the first centile for age or < 500 g birth weight are rare, making prognostication about their outcomes difficult. However, > 300 such babies are born in California each year, providing an opportunity to study their outcomes in this population-based cohort.

ProSGA and ProLBW were markedly different in their antenatal risk factors to AGA and VLBW infants. In addition to being smaller and more growth restricted than other VLBW infants, the ProSGA and ProLBW infants were significantly less likely to receive antenatal steroids and significantly less likely to be delivered by cesarean section. The nature of the retrospective data collection does not allow identification of the reasons for these difference in prenatal management, but it may reflect a belief that such interventions were unlikely to benefit infants with such poor chances of survival. Similarly, the decreased incidence of prolonged ROM (despite a similar rate of preterm ROM) may suggest that attempts to delay delivery (for example, to allow steroids to be given) were less likely to be carried out in ProSGA and ProLBW infants. The lower rate of fetal distress in ProSGA and ProLBW than in other VLBW infants may also reflect more extensive attempts to delay delivery in VLBW infants.

Despite the lower rates of fetal distress, Apgar scores were significantly reduced in ProSGA and ProLBW infants. This was mirrored by very high mortality in those infants prior to NICU admission. Approximately 21% of infants weighing 300 to 500 g at birth survived to hospital discharge, similar to the 17% report by Lucey *et al.*[2] for infants of birth weight 400 to 500 g in the late 1990s.

Over half of the ProSGA and ProLBW die before NICU admission, compared with only 3% of AGA or VLBW infants. This is similar to previous reports. Data from the Vermont Oxford Network from the 1990s showed that 52% of infants of birth weight 400 to 500 g died in the delivery room.[2] In a European study, mortality in L&D was 100% for 22 weeks gestation infants, 80% at 23 weeks gestation and 36% at 24 weeks gestation, and the majority (89%) of the deaths in L&D among these infants was due to a decision to withdraw or limit care.[10] These deaths are the lowest when mothers are transferred to a higher level of care before delivery,[11] perhaps because the transfer is a marker for an increased aggressiveness in providing vigorous prenatal and postnatal care to these infants.

In our study, ProSGA and ProLBW infants continued to be at elevated risk of death after NICU admission compared with AGA VLBW infants. However, the majority of deaths in AGA and VLBW infants occur after 12 h of age, and the majority of deaths in ProSGA and ProLBW infants occur before 12 h of age.

Mortality, poor growth and many neonatal morbidities were more common in ProSGA and ProLBW than in AGA and VLBW infants. Some of these poorer outcomes were completely explainable by difference in antenatal risk factors, gestational age and body size at birth, whereas some were not. For example, the odds of death were increased 30-fold in ProSGA infants and

Table 3. Odds ratios (ORs) for different outcomes between the ProSGA cohort and the comparison AGA cohort and between the ProLBW cohort and the comparison AGA cohort

Comparison	*Profoundly SGA (BW < 1st centile) vs AGA (5–95th centile)*				*Profoundly LBW (300–500 g) vs VLBW (500–1500 g)*			
Model	*Crude OR*[a]	*Adjusted OR*[b]	*Adjusted OR*[c]	*Adjusted OR*[d]	*Crude OR*[a]	*Adjusted OR*[b]	*Adjusted OR*[e]	*Adjusted OR*[f]
Adjustments	*None*	*OB factors and GA*	*OB factors and BW*	*OB, GA and BW*	*None*	*OB factors and GA*	*OB factors and BWZ*	*OB, GA and BWZ*
Mortality								
Died prior to NICU admission	49.8 (41.9–59.4) $P < 0.0001$	12.9 (10.0–16.7) $P < 0.0001$	3.28 (2.42–4.46) $P < 0.0001$	5.1 (3.7–7.1) $P < 0.0001$	33.5 (30.1–37.3) $P < 0.0001$	5.1 (4.4–6.0) $P < 0.0001$	3.2 (2.7–3.7) $P < 0.0001$	3.9 (3.3–4.6) $P < 0.0001$
Died by 12 h	39.4 (33.2–46.9) $P < 0.0001$	11.8 (9.3–14.9) $P < 0.0001$	3.36 (2.58–4.37) $P < 0.0001$	5.3 (4.0–7.1) $P < 0.0001$	29.4 (26.5–32.6) $P < 0.0001$	0.39 (0.35–0.43) $P < 0.0001$	3.3 (2.8–3.8) $P < 0.0001$	4.2 (3.6–4.9) $P < 0.0001$
Died before discharge home	29.8 (24.0–37.4) $P < 0.0001$	10.5 (8.2–13.5) $P < 0.0001$	2.73 (2.14–3.52) $P < 0.0001$	4.0 (3.1–5.2) $P < 0.0001$	24.2 (21.5–27.2) $P < 0.0001$	5.7 (5.0–6.5) $P < 0.0001$	2.7 (2.4–3.1) $P < 0.0001$	3.4 (2.9–3.9) $P < 0.0001$
Died between admission and 12 h	9.5 (6.6–13.5) $P < 0.0001$	4.9 (3.2–7.1) $P < 0.0001$	1.80 (1.14–2.81) $P = 0.0122$	2.8 (1.7–4.5) $P < 0.0001$	10.7 (8.7–13.1) $P < 0.0001$	3.4 (2.7–4.3) $P < 0.0001$	2.1 (1.7–2.7) $P < 0.0001$	2.6 (2.0–3.4) $P < 0.0001$
Died between 12 h and discharge home	9.5 (7.2–12.5) $P < 0.0001$	6.0 (4.5–8.1) $P < 0.0001$	1.42 (1.06–1.91) $P = 0.0206$	2.3 (1.7–3.1) $P < 0.0001$	9.5 (8.2–11.0) $P < 0.0001$	3.7 (3.1–4.3) $P < 0.0001$	1.6 (1.4–1.9) $P < 0.0001$	2.0 (1.7–2.4) $P < 0.0001$
Growth[g]								
Discharge weight *Z*-score < 5th centile	11.9 (6.43–24.49) $P < 0.0001$	25.7 (13.7–53.7) $P < 0.0001$	5.3 (2.8–11.0) $P < 0.0001$	1.4 (0.7–3.1) $P = 0.32$	9.1 (7.0–12.0) $P < 0.0001$	14.3 (10.9–19.0) $P < 0.0001$	3.19 (2.44–4.24) $P < 0.0001$	2.75 (2.02–3.79) $P < 0.0001$
Discharge weight *Z*-score < 10th centile	66 (15–1167) $P < 0.0001$	131 (29–2308) $P < 0.0001$	32.2 (7.1–568) $P < 0.0001$	8.4 (1.8–150) $P = 0.0031$	10.8 (7.5–16.0) $P < 0.0001$	18.2 (12.6–27.4) $P < 0.0001$	4.76 (3.30–7.15) $P < 0.0001$	4.00 (2.68–6.16) $P < 0.0001$
Fall in weight *Z*-score > 0.67	0.22 (0.14–0.34) $P < 0.0001$	0.68 (0.40–1.17) $P = 0.16$	10.0 (6.3–15.9) $P < 0.0001$	3.1 (1.8–5.1) $P < 0.0001$	0.10 (0.08–0.13) $P < 0.0001$	0.58 (0.44–0.78) $P = 0.0003$	4.16 (3.27–5.26) $P < 0.0001$	1.93 (1.46–2.55) $P < 0.0001$
Fall in weight *Z*-score > 1.00	0.26 (0.16–0.40) $P < 0.0001$	0.91 (0.52–1.58) $P = 0.75$	11.9 (7.3–18.9) $P < 0.0001$	4.2 (2.4–7.1) $P < 0.0001$	0.11 (0.09–0.14) $P < 0.0001$	0.70 (0.51–0.94) $P = 0.0197$	5.24 (4.08–6.69) $P < 0.0001$	2.60 (1.93–3.47) $P < 0.0001$
Morbidities								
Early sepsis (< 3 days)	0.53 (0.13–1.40) $P = 0.23$	0.33 (0.08–0.89) $P = 0.0243$	0.49 (0.12–1.31) $P = 0.18$	0.54 (0.13–1.47) $P = 0.25$	0.83 (0.45–1.85) $P = 0.50$	0.42 (0.23–0.71) $P = 0.0006$	0.45 (0.25–0.77) $P = 0.0023$	0.55 (0.29–0.93) $P = 0.0244$
Late bacterial sepsis (>3 days)	1.96 (1.37–2.74) $P = 0.0003$	1.45 (1.01–2.04) $P = 0.0403$	2.48 (1.72–3.51) $P < 0.0001$	1.06 (0.73–1.53) $P = 0.76$	2.79 (2.30–3.36) $P < 0.0001$	1.39 (1.14–1.69) $P = 0.0013$	0.94 (0.77–1.15) $P = 0.55$	1.08 (0.87–1.31) $P = 0.50$
Late fungal sepsis (>3 days)	2.86 (1.01–6.34) $P = 0.0481$	1.64 (0.57–3.70) $P = 0.33$	3.93 (1.37–8.80) $P = 0.0142$	1.05 (0.34–2.62) $P = 0.93$	2.69 (1.38–4.71) $P = 0.0055$	0.92 (0.47–1.64) $P = 0.79$	0.55 (0.28–1.01) $P = 0.0521$	0.71 (0.35–1.29) $P = 0.27$
Late sepsis (>3 days) (bacterial or fungal)	1.91 (1.34–2.66) $P = 0.0005$	1.39 (0.97 = 1.96) $P = 0.07$	2.42 (1.68–3.42) $P < 0.0001$	1.00 (0.68–1.43) $P = 0.99$	2.77 (2.29–3.31) $P < 0.0001$	1.35 (1.11–1.63) $P = 0.0031$	0.90 (0.74–1.10) $P = 0.31$	1.04 (0.85–1.26) $P = 0.73$
CLD	2.56 (1.97–3.37) $P < 0.0001$	1.41 (1.07–1.88) $P = 0.0137$	2.65 (2.02–3.50) $P < 0.0001$	0.63 (0.48–0.85) $P = 0.0025$	3.28 (2.86–3.78) $P < 0.0001$	1.09 (0.94–1.27) $P = 0.25$	0.54 (0.47–0.63) $P < 0.0001$	0.61 (0.53–0.71) $P < 0.0001$
Severe ROP	4.97 (3.30–7.43) $P < 0.0001$	2.69 (1.73–4.16) $P < 0.0001$	5.62 (3.67–8.53) $P < 0.0001$	1.01 (0.64–1.59) $P = 0.97$	6.95 (5.59–8.61) $P < 0.0001$	1.93 (1.51–2.46) $P < 0.0001$	0.58 (0.46–0.73) $P < 0.0001$	0.88 (0.69–1.13) $P = 0.32$
ROP surgery or VEGF treatment	5.56 (3.67–8.34) $P < 0.0001$	2.89 (1.84–4.50) $P < 0.0001$	6.44 (4.20–9.79) $P < 0.0001$	1.10 (0.69–1.75) $P = 0.69$	6.56 (5.23–8.18) $P < 0.0001$	1.68 (1.30–2.16) $P < 0.0001$	0.48 (0.37–0.61) $P < 0.0001$	0.76 (0.59–0.98) $P = 0.0369$
Grade 3 or 4 IVH	1.50 (1.03–2.10) $P = 0.0308$	0.80 (0.54–1.5) $P = 0.23$	1.16 (0.78–1.67) $P = 0.45$	0.82 (0.55–1.20) $P = 0.32$	2.33 (1.92–2.80) $P < 0.0001$	0.76 (0.61–0.92) $P = 0.0060$	0.52 (0.43–0.64) $P < 0.0001$	0.74 (0.60–0.91) $P = 0.0039$
PVL	0.15 (0.08–0.66) $P = 0.0063$	0.12 (0.01–0.51) $P = 0.0012$	0.20 (0.01–0.89) $P = 0.0298$	0.11 (0.01–0.51) $P = 0.0013$	1.24 (0.78–1.85) $P = 0.35$	0.71 (0.45–1.08) $P = 0.11$	0.60 (0.37–0.92) $P = 0.0166$	0.69 (0.43–1.05) $P = 0.09$
NEC	1.38 (0.92–2.01) $P = 0.12$	1.07 (0.71–1.56) $P = 0.72$	1.45 (0.95–2.13) $P = 0.08$	0.85 (0.55–1.27) $P = 0.45$	1.39 (1.09–1.74) $P = 0.0092$	0.83 (0.65–1.06) $P = 0.13$	0.63 (0.49–0.80) $P = 0.0001$	0.67 (0.52–0.85) $P = 0.0008$
Surgical NEC	1.81 (1.02–2.95) $P = 0.0425$	1.17 (0.66–1.93) $P = 0.56$	2.36 (1.30–3.93) $P = 0.0064$	0.94 (0.51–1.62) $P = 0.83$	1.55 (1.07–2.17) $P = 0.0222$	0.77 (0.42–1.08) $P = 0.13$	0.56 (0.38–0.80) $P = 0.0009$	0.63 (0.42–0.89) $P = 0.0088$
Isolated GI perforation	1.51 (0.91–2.34) $P = 0.11$	0.80 (0.48–1.6) $P = 0.34$	1.48 (1.31–1.68) $P < 0.0001$	0.50 (0.29–0.81) $P = 0.0041$	1.70 (1.26–2.24) $P = 0.0008$	0.64 (0.47–0.85) $P = 0.0016$	0.40 (0.29–0.53) $P < 0.0001$	0.47 (0.34–0.63) $P < 0.0001$

Abbreviations: AGA, appropriate for gestational age; BW, birth weight; BWZ, birth weight *Z*-score; CLD, chronic lung disease; GI, gastrointestinal; IVH, intraventricular hemorrhage; LBW, low birth weight; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OB, obstetric; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SGA, small for gestational age; VEGF, vascular endothelial growth factor; VLBW, very low birth weight. Data are given as crude unadjusted ORs (model no. 1), adjusted for OB factors (gender, C/section, multiple gestation) and gestational age (model no. 2), adjusted for OB factors and BW or birth size (model no. 3) and adjusted for OB factors, gestational age and BW or birth size (model no. 4). ORs significantly different from model no. 1 are shown emboldened. [a]Unadjusted odds ratio (95% confidence interval). [b]OR adjusted for gender, antenatal steroids, C/section, multiple gestation and gestational age. [c]OR adjusted for gender, antenatal steroids, C/section, multiple gestation and BW. [d]OR adjusted for gestational age, gender, antenatal steroids, C/section, multiple gestation, gestational age and BW. [e]OR adjusted for gestational age, gender, antenatal steroids, C/section, multiple gestation and BWZ. [f]OR adjusted for gestational age, gender, antenatal steroids, C/section, multiple gestation, gestational age and BWZ. [g]Among survivors.

Table 4. Results of logistic regression of the effect on gender, gestational age, birth weight, birth weight *Z*-score, antenatal steroids, C/section and multiple birth status on mortality in the entire cohort and in the ProSGA and the ProLBW cohorts

Factor	*Overall mortality*	*Time of death*		
		In DR	*Admit—12 h*	*After 12 h*
Entire cohort				
Gender	0.10 (0.08–0.12) $P < 0.0001$	0.05 (0.04–0.07) $P < 0.0001$	0.14 (0.10–0.21) $P < 0.0001$	0.21 (0.17–0.25) $P < 0.0001$
Gestational age	0.96 (0.95–0.97) $P < 0.0001$	0.94 (0.93–0.95) $P < 0.0001$	0.96 (0.95–0.97) $P < 0.0001$	0.97 (0.96–0.98) $P < 0.0001$
Birth weight	1.2e-23 (1e-25–1e-21) $P < 0.0001$	2e-31 (1e-34–5e-41) $P < 0.0001$	2e-17 (8e-14–8e-21) $P < 0.0001$	8e-13 (1e-14–6e-11) $P < 0.0001$
Birth weight *Z*-score	5e21 (6e19–5e23) $P < 0.0001$	2e36 (6e32–7e39) $P < 0.0001$	564 (136–2290) $P < 0.0001$	79 (37–167) $P < 0.0001$
Antenatal steroids	0.39 (0.37–0.42) $P < 0.0001$	0.20 (0.17–0.22) $P < 0.0001$	0.35 (0.30–0.42) $P < 0.0001$	0.57 (0.52–0.62) $P < 0.0001$
C/section	0.75 (0.70–0.80) $P < 0.0001$	0.25 (0.22–0.28) $P < 0.0001$	0.80 (0.68–0.94) $P = 0.0075$	0.99 (0.92–1.08) $P =$ NS
Multiple gestation	1.16 (1.08–1.25) $P = 0.0004$	1.00 (0.87–1.15) $P =$ NS	1.07 (0.89–1.28) $P =$ NS	1.15 (1.07–1.26) $P = 0.0004$
ProSGA				
Gender	0.83 (0.48–1.44) $P =$ NS	0.74 (0.45–1.21) $P =$ NS	0.92 (0.39–2.18) $P =$ NS	0.92 (0.50–1.67) $P =$ NS
Gestational age	0.96 (0.94–0.99) $P = 0.0022$	0.93 (0.90–0.96) $P < 0.0001$	0.90 (0.75–0.95) $P < 0.0001$	0.99 (0.97–1.01) $P =$ NS
Birth weight	0.0008 (0.00–1.47) $P = 0.06$	0.002 (0.00–1.57 $P = 0.07$	4e-10 (5e-5–1e-15) $P = 0.0003$	0.08 (0.00–366) $P =$ NS
Antenatal steroids	0.16 (0.07–0.34) $P < 0.0001$	0.24 (0.14–0.40) $P < 0.0001$	0.68 (0.26–1.85) $P =$ NS	0.38 (0.16–0.87) $P = 0.0209$
C/section	0.21 (0.08–0.49) $P = 0.0002$	0.23 (0.14–0.39) $P < 0.0001$	0.23 (0.08–0.63) $P = 0.0044$	0.66 (0.23–1.76) $P =$ NS
Multiple gestation	2.41 (1.17–5.37) $P = 0.0158$	1.49 (0.89–2.54) $P =$ NS	0.67 (0.23–1.77) $P =$ NS	2.31 (1.06–5.39) $P = 0.0354$
ProLBW				
Gender	0.99 (0.64–1.33) $P =$ NS	0.74 (0.56–0.98) $P = 0.0385$	0.92 (0.59–1.41) $P =$ NS	0.91 (0.66–1.25) $P =$ NS
Gestational age	0.96 (0.95–0.97) $P = 0.0021$	0.92 (0.09–0.94) $P < 0.0001$	0.96 (0.73–0.98) $P < 0.0001$	0.98 (0.97–0.99) $P = 0.0014$
Birth weight *Z*-score	0.11 (0.05–0.21) $P < 0.0001$	0.10 (0.03–0.15) $P < 0.0001$	0.28 (0.11–073) $P = 0.0004$	0.21 (0.09–0.45) $P < 0.0001$
Antenatal steroids	0.25 (0.18–0.34) $P < 0.0001$	0.19 (0.15–0.26) $P < 0.0001$	0.27 (0.17–0.42) $P = 0.0004$	0.65 (0.45–0.94) $P = 0.0235$
C/section	0.32 (0.22–0.47) $P < 0.0001$	0.18 (0.14–0.25) $P < 0.0001$	0.59 (0.36–0.95) $P = 0.0308$	0.75 (0.50–1.12) $P =$ NS
Multiple gestation	1.74 (1.24–2.46) $P = 0.010$	0.91 (0.68–1.23) $P =$ NS	1.25 (0.79–1.98) $P =$ NS	1.92 (1.34–2.76) $P = 0.004$

Abbreviations: DR, delivery room; NS, not significant.

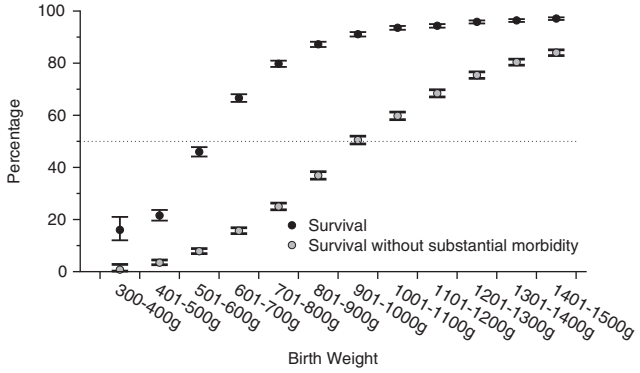

Figure 3. Survival rates and survival without substantial mortality for different birth weight strata. Error bars represent 95% confidence intervals of the mean.

24-fold in ProLBW. Even after accounting for differences in antenatal risk factors, gestational age and birth size, odds of mortality was 4-fold higher in ProSGA infants and 3.4-fold higher in ProLBW. In contrast, for example, the increase in late fungal sepsis in ProSGA and ProLBW infants was not seen after correcting for gestational age and birth size. Finally, the increased risk of gastrointestinal perforation in ProSGA and ProLBW infants was reversed after correcting for gestation age and birth weight. The increased risk of gastrointestinal perforation was, therefore, less than would be predicted based on differences in gestational age and birth size.

In crude unadjusted analysis, the rate of postnatal growth failure (a fall in weight *Z*-score during admission >0.67 or >1.0) was lower in ProSGA and ProLBW infants. This result is presumably due to greater regression to the mean in groups whose initial weight *Z*-score is further from the mean (ProSGA and ProLBW) than in groups whose initial weight *Z*-score is closer to the mean (AGA and VLBW). This is supported by the analysis showing that rates of postnatal growth failure were higher in ProLBW and ProSGA infants after correcting for birth weight or birth weight *Z*-score.

When the factors affecting survival were examined using logistic regression model, survival among the entire cohort was significantly higher in females, older gestational age, larger birth weight and larger birth weight *Z*-score, those who received antenatal steroids, those delivered by cesarean section and in singletons. Similar factors have been shown to be associated with survival in a separate prospective analysis of CPQCC data from 2005 to 2008 for infants of gestational age 22 to 25 weeks.[6]

Our data suggest that being a singleton was associated with improved rates of survival compared with multiple gestation, consistent with previous CPQCC data.[6] However, this effect was limited to mortality after 12 h of age.

Males are at increased risk of mortality than females, and this has also been previously reported for infants <500 g at birth,[2] or <25 weeks gestation [6]. Although we were able to demonstrate improved survival in females for the entire cohort, we did not see a significant effect for the ProLBW or ProSGA infants alone.

Antenatal steroids are known to be associated with improved survival in preterm infants, although there are relatively few data for the smallest and most preterm infants.[12,13] Our data and previous CPQCC data suggest that the benefit seen in younger and smaller infants is similar to that seen in their larger and more mature peers.[6] Data on the effect of cesarean section of survival of preterm infants are contradictory.[14,15] However, data on 401 to 500 g infants suggests that those born by vaginal delivery are more likely to die in L&D and are less likely to survive to discharge.[2] These results are consistent with our study, where the effect of cesarean section on survival was most significant prior to NICU admission, less significant between NICU admission and 12 h of age and had no significant effect after 12 h of age.

It is interesting to note the positive associations of cesarean section delivery and antenatal steroids on survival, even in the ProSGA and ProLBW infants, especially as they were much less likely to receive these interventions than the AGA or VLBW infants. These associations should be treated cautiously, as causality cannot be assumed. Administration of antenatal steroids to these highest risk infants and willingness to deliver by cesarean section may be the markers for centers with more aggressive approaches to the prenatal and antenatal management of these infants. Conversely, centers that do not give antenatal steroids or deliver these infants by cesarean section may be less aggressive in delivery room resuscitation or more likely to limit or withdraw care subsequent to NICU admission. Given the low survival rates, and lower rates of survival without substantial morbidity in these infants, parents and care givers must balance any possible improvements in neonatal outcomes with the increased risk exposure for mothers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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