Elinor Charles, Katie A. Hunt, Christopher Harris, Ann Hickey and Anne Greenough*

Small for gestational age and extremely low birth weight infant outcomes

https://doi.org/10.1515/jpm-2018-0295
Received September 7, 2018; Accepted September 25, 2018

Abstract

Background: Small for gestational age (SGA) infants are less likely to develop respiratory distress syndrome (RDS), but more likely to develop bronchopulmonary dysplasia (BPD) and have a higher mortality. Our aim was to focus on outcomes of those with a birth weight less than or equal to 750 g.

Methods: The mortality, BPD severity, necrotising enterocolitis (NEC), home oxygen requirement and length of hospital stay were determined according to SGA status of all eligible infants in a 5-year period admitted within the first 24 h after birth.

Results: The outcomes of 84 infants were assessed, and 35 (42%) were SGA. The SGA infants were more mature ($P < 0.001$), had a lower birth weight centile ($P < 0.001$) and a greater proportion exposed to antenatal corticosteroids ($P = 0.022$). Adjusted for gestational age (GA), there was no significant difference in mortality between the two groups ($P = 0.242$), but a greater proportion of the SGA infants developed severe BPD ($P = 0.025$). The SGA infants had a lower weight z-score at discharge (–3.64 vs. –1.66) ($P = 0.001$), but a decrease in z-score from birth to discharge was observed in both groups (median –1.53 vs. –1.07, $P = 0.256$).

Conclusions: Despite being more mature, the SGA infants had a similar mortality rate and a greater proportion developed severe BPD.

Keywords: bronchopulmonary dysplasia; extremely low birth weight; necrotising enterocolitis; small for gestational age.

Introduction

Small for gestational age (SGA) infants have been shown to be less likely to develop respiratory distress syndrome (RDS), possibly due to intra-uterine stress leading to accelerated lung maturation [1]. Other outcomes, however, appear to be worse for those born SGA, that is, having a birth weight below the tenth centile for their gestational age (GA) and sex [1–3]. Amongst infants born at less than or equal to 36 weeks of gestation, the SGA infants had a higher mortality, a significantly higher risk of developing chronic lung disease and a longer hospital stay [1]. Furthermore, in infants born with a very low birth weight, the SGA group had increased risks of mortality and severe bronchopulmonary dysplasia (BPD) [2]. There has, however, been little focus on whether amongst infants with a birth weight less than or equal to 750 g, being born SGA influences mortality or morbidity. The aim of this study was to determine whether amongst such infants, those who were SGA had poorer outcomes than those who were born with a weight appropriate for their GA.

Materials and methods

A retrospective study of medical records and the BadgerNet Neonatal Electronic Patient Records at a tertiary neonatal intensive care unit (NICU) was undertaken. This study was undertaken as a clinical audit and as a consequence ethical approval was not required. All infants with a birth weight of 750 g or less, who were either born at or transferred to the hospital within the first 24 h after birth and admitted to the NICU for ongoing care between 2012 and 2016 were included in the study. Infants who died on the labour suite were not included.

Information extracted from the medical records included age at extubation, the occurrence of BPD, severe BPD and necrotising enterocolitis (NEC), whether the infants had had naso-jejunal feeding, their weight at birth and discharge and the change in birth weight

***Corresponding author: Professor Anne Greenough,** Neonatal Intensive Care Centre, 4th Floor Golden Jubilee Wing, King's College Hospital NHS Foundation Trust, Denmark Hill, London, SE5 9RS, UK; MRC-Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, London, UK; Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK; and National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK, Tel.: +0203 299 3037, Fax: +0203 299 8284, E-mail: anne.greenough@kcl.ac.uk

Elinor Charles, Katie A. Hunt and Christopher Harris: MRC-Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, London, UK; and Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

Ann Hickey: Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK

centile from birth to discharge and the cause of any mortality. BPD was defined as an ongoing oxygen requirement at 28 days of age. Those infants requiring positive pressure support or ≥30% oxygen at 36 weeks post conceptional age were classified as having severe BPD [4]. NEC was diagnosed if there were both clinical signs (abdominal distension, abdominal discolouration, clinical instability, bilious aspirates and/or vomiting) and radiological abnormalities (pneumatosis intestinalis, gas in the hepato-biliary tract or a pneumoperitoneum) [5]. In addition, a surgical review had been undertaken and the infants had received a minimum of 5 days of treatment with antibiotics whilst being kept nil by mouth. Centiles and z-scores were calculated using UK World Health Organization (WHO) preterm reference ranges [6], and infants were divided into SGA and appropriate for gestational age (AGA) groups. SGA infants were defined as those below the tenth centile for sex and GA and AGA as those between the tenth and ninetieth centile.

Respiratory protocol

Infants of less than 32 weeks of GA who required intubation and ventilation in the delivery room were started on a peak inflation pressure (PIP) of 20–25 cm H_2O, a positive end expiratory pressure (PEEP) of 4–5 cm H_2O and a fraction of inspired oxygen (FiO_2) of 0.21–0.30. They were given surfactant when stabilised. On transfer to the neonatal unit, they were ventilated on pressure-controlled time-cycled or assist-control ventilation using an SLE 5000 neonatal ventilator or an SLE 2000 infant ventilator (SLE, Croydon, UK). In the latter 2 years, volume-targeted ventilation was also used. All infants were ventilated with Cole's shouldered endotracheal tubes which have been shown to have minimal or no leaks [7]. The supplementary oxygen was modified to achieve oxygen saturation levels between 92 and 95%. Infants who required a PIP exceeding 25 cm H_2O were transferred to high frequency oscillation. Extubation was attempted when the FiO_2 was ≤30% and the PIP had been reduced below 18 cm H_2O. Caffeine was commenced in the first 24 h. The nurses recorded hourly on observation charts, the level of respiratory support required by the infant. Infants were considered for supplementary oxygen at home when they had reached full oral feeds at 3 hourly intervals, but still required supplementary oxygen. They were sent home on supplementary oxygen if they were stable and had suitable home conditions.

Feeding protocol

Our feeding policy followed the East of England guidelines with clinician's discretion exercised on increasing feeds in line with the protocol [8]. In the study population, colostrum was encouraged for mouth care from day 1. Trophic feeds (<20 mL/kg/day) were started as soon as mother's milk was available and clinical stability was achieved. If mother's milk was not available and permission was given, donor milk was used. All of the infants in this study fulfilled the criteria for donor milk as they were born at a GA of less than 32 weeks. For infants whose mothers did not provide maternal milk, donor milk was continued for 14–21 days, when a transition to preterm formula was made to promote growth. Parenteral nutrition was commenced as early as possible post-delivery and standard bags were available out of hours. In infants with feed intolerance or dysmotility, concentrated parenteral nutrition at 50% of the total fluid intake was continued to ensure adequate calorie intake until growth and absorption were established. Using concentrated parenteral nutrition, up to 75% of calorie requirement can be given in 50% of the fluid volume. Fortifier was added to the breast milk at the consultant's discretion, when infants achieved feed volumes of 150 mL/kg/day. Enteral feeds of 180 mL/kg/day of fortified maternal breast milk were aimed for in all infants. For formula-fed infants, volumes ranged from 150 mL/kg to 180 mL/kg depending on calorie content and growth. Energy dense term formula, e.g. infatrini, was considered for those approaching term corrected age and whose intake was limited by ongoing respiratory distress associated with BPD. Naso-jejunal feeding was considered for infants where feeding advancement was limited by either respiratory disease or gastro-oesophageal reflux. A multi-disciplinary nutrition team including a paediatric dietician and gastroenterologist reviewed all infants weekly to optimise nutrition and growth. Breastfeeding was actively encouraged by a dedicated NICU breast-feeding support worker; a specialised speech and language therapist was available.

Statistical analysis

The data were shown to be non-normally distributed and hence the Mann-Whitney *U*-test or chi-square (χ^2) test was used as appropriate to assess whether differences in the demographics were statistically significant. Multiple linear regression or binary logistic regression as appropriate was used to adjust for differences in GA in the outcomes between the two groups. Statistical analysis was performed using IBM SPSS statistics version 24.

Results

Demographics

Thirty-five (42%) of the 84 infants in the study were SGA. The groups differed significantly at birth with regard to GA ($P < 0.001$), birth weight ($P = 0.001$) and birth weight z-score ($P < 0.001$) (Table 1). A greater proportion of the SGA infants had mothers who had hypertension ($P \leq 0.001$), received antenatal steroids ($P = 0.022$), had abnormal umbilical Doppler results and had a caesarean section delivery ($P \leq 0.001$). All of the infants were intubated and ventilated in the delivery suite and given surfactant.

There were no significant differences in the mortality rate between the two groups ($P = 0.242$). Eleven infants of the SGA group died. Their causes of death were extreme prematurity/hypoxic respiratory failure (n = 7), respiratory failure secondary to BPD (n = 2), pulmonary haemorrhage (n = 1) and withdrawal of care following hypoxic brain injury after cardiac arrest (n = 1). Fifteen infants of the AGA group died. Their causes of death were extreme prematurity/hypoxic respiratory failure (n = 7), respiratory failure

Table 1: Demographics according to SGA status.

	SGA (n=35)	AGA (n=49)	P-Value
Antenatal corticosteroids	33 (94.3%)	38 (78%)	0.022
Maternal hypertension	17 (48.6%)	4 (8%)	<0.001
Abnormal Dopplers[a]			
Normal	8 (23%)	33 (67%)	<0.001
Abnormal	25 (71%)	1 (2%)	
Mode of delivery			
SVD[b]/instrumental	11 (31%)	45 (92%)	<0.001
Caesarean section	24 (69%)	4 (8%)	
Gestational age at birth, weeks	26.9 (23.4–31.9)	24.3 (22.3–26.7)	<0.001
Sex	21 (60%)	26 (53%)	0.528
Birth weight, g	598 (450–732)	662 (510–750)	0.001
z-Score at birth	−2.22 (−3.64 to −1.38)	−0.64 (−1.31 to +0.6)	<0.001
Birth centile	1 (0.05–8)	26 (10–73)	<0.001
Surfactant	35 (100%)	49 (100%)	

The results are demonstrated as median (range) or n (%). [a]Data were not available for all infants. [b]Spontaneous vaginal delivery.

secondary to BPD (n=3), pulmonary haemorrhage (n=2), withdrawal of care following bilateral haemorrhagic parenchymal infarcts (n=1), *Pseudomonas* sepsis (n=1) and NEC (n=1). All infants who survived to 36 weeks corrected GA had BPD. A greater proportion of the SGA infants developed severe BPD (P=0.025) (Table 2), but there was no significant difference in the length of hospital stay or in the proportions of the two groups who required home oxygen (Table 2).

The SGA infants had a significantly lower weight z-score at discharge (P=0.001). A decrease in weight z-score from birth to discharge was observed in both groups and the change in weight z-score did not differ significantly between the two groups (P=0.256) (Table 3).

Table 2: Mortality and respiratory morbidity according to SGA status.

	SGA (n=35)	AGA (n=49)	Odds ratio or risk estimate for 95% confidence intervals	P-Value adjusted for gestational age
Mortality	11 (31%)	15 (31.5%)	0.75 (0.60–7.40)	0.242
Age at death, days	36 (1–536)	14 (0–151)	40 (−80 to 160)	0.50
Severe BPD[a]	17 (70.8%)	22 (64.7%)	2.39 (1.35–88.26)	0.025
Length of hospital stay	126.5 (63–404)	130.5 (89–309)	53 (−2.29 to 81.09)	0.064
Home oxygen	16 of 24 (67%)	24 of 34 (71%)	1.32 (0.56–24.73)	0..173

The results are expressed as median (range) or n (%). [a]Of all infants surviving to 36 weeks of gestation.

Table 3: NICU course and discharge outcome.

	SGA (n=35)	AGA (n=49)	Odds ratio or risk estimate (95% confidence interval)	P-Value adjusted for GA
NEC	8/35 (23%)	10/49 (20%)	0.5 (0.1–2.5)	0.349
Age at full enteral feeds, days	53.5 (26–172)	47.5 (11–184)	38.2 (9.1–67.2)	0.011
Required NJ feeding	3/35 (8.6%)	7/49 (14%)	2.3 (0.28–18.7)	0.443
Breastfeeding on discharge home	6/24 (25%)	12/34 (35%)	1.6 (0.33–8.0)	0.56
Any breast milk at discharge home	10/24 (42%)	20/34 (59%)	2.5 (0.57–10.6)	0.23
Length of hospital stay (days) in those surviving to discharge	126.5 (63–404)	130.5 (89–309)	39.4 (−2.2–81)	0.064
Weight z-Score at discharge	−3.64 (−4.93 to −1.73)	−1.66 (−4.91 to 0.65)	−1.5 (−2.4 to −0.67)	0.001
Change in weight z-Score from birth to discharge	−1.53 (−4.01 to 0.54)	−1.065 (−4.72 to 1.34)	0.47 (−0.35 to 1.30)	0.256

Data are presented as n (%) or median (range). NJ, naso-jejunal.

Discussion

We have demonstrated that SGA infants were more likely to develop severe BPD than AGA infants (P = 0.025), despite being more mature at birth and a greater proportion being exposed to antenatal corticosteroids. An increased risk of moderate to severe BPD (23% vs. 9%, respectively, P < 0.001) [9] was found in a study of infants born before 32 weeks of gestation amongst those with antenatal growth restriction compared to those without [9]. Furthermore, amongst infants born before 28 weeks of gestation, fetal growth restriction was highly predictive of BPD after adjustment for other risk factors [10]. Our study uniquely reports an increased risk of severe BPD in SGA infants with a birth weight less than 750 g. Fetal growth restriction in animal models has been reported to result in structural changes to the lungs, that is, fewer and larger alveoli and a thickened blood-air barrier [11, 12]. Proposed mechanisms include malnutrition [12, 13] and increased exposure to proinflammatory cytokines both pre- and immediately postnatally [14, 15]. Nevertheless, we did not demonstrate that the SGA infants compared to the AGA infants were more likely to require "home oxygen" which may reflect their greater maturity at birth.

We found no significant difference in the mortality rate between the two groups, even when adjusted for GA. This finding is supported by a previous report of no significant difference in mortality between the SGA and AGA groups born between 26 and 28 weeks of GA [16], but they differed from our study population in that they had not been routinely exposed to antenatal steroids and postnatal surfactant. In contrast, in more mature infants, SGA has been frequently associated with an increased mortality [1, 2, 17].

The weight z-scores of infants born with a birth weight between 500 g and 749 g had been reported to fall by 1.10 from admission to discharge [18]. In 2013, half of the premature infants born weighing less than 1500 g in North American hospitals were discharged with a weight under the tenth centile for their age [19]. Low GA, low birth weight, the need for assisted ventilation on the first day after birth and the development of BPD have all been independently associated with poor growth [20, 21]. Although previous studies have suggested that SGA preterm infants experience a higher incidence of postnatal growth failure than AGA infants [22], we did not find this in our infants all who had a birth weight less than 750 g. Indeed, we did not find any significant difference in the changes in weight z-scores between AGA and SGA infants. We suggest our results may reflect a relatively aggressive nutritional policy.

Our study has strengths and some limitations. Previous studies have been criticised for failing to account for differences in GA and birth weight across cohorts and between comparison groups [1, 2]. We assessed the outcomes of all infants with a birth weight less than 750 g. Our SGA group had a significantly higher median GA than our AGA group; we, therefore, adjusted for GA when determining the impact of being SGA at birth on outcomes. Whilst previous studies have focused on very low birth weight infants (<1500 g) and premature infants (<36 weeks), this is the first study to look specifically at the effect of SGA in the extremely low birth weight infant, i.e. a birth weight less than 750 g.

In conclusion, amongst infants with a birth weight less than or equal to 750 g, those born SGA despite being on average 2 weeks more mature, had a similar mortality rate to the AGA infants. In addition, a greater proportion of the SGA infants had severe BPD and a similar length of stay to the AGA infants. These results should help to inform counselling of parents expecting an SGA, prematurely born infant.

Author contributions: AG and AH designed the study. EC collected the data. EC, KH, CH and AG analysed the data. All authors were involved in the production of the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: The research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, Grant Number: N/A. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organisation(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Sharma P, McKay K, Rosenkrantz TS, Hussain N. Comparisons of mortality and pre-discharge respiratory outcomes in small-for-gestational-age and appropriate-for-gestational-age premature infants. BMC Pediatr. 2004;4:9.
2. Tsai LY, Chen YL, Tsou KI, Mu SC, Taiwan Premature Infant Developmental Collaborative Study Group. The impact of

small-for-gestational-age on neonatal outcome among very-low-birth-weight infants. Pediatr Neonatol. 2015;56:101–7.
3. Tannirwar S, Kadam S, Pandit A, Vaidya U, Parikh T, Ankit S. Comparisons of mortality and pre-discharge respiratory morbidities in small for gestational age and appropriate-for gestational age premature infants – an Indian experience. IJN. 2016;7:1–6.
4. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723–9.
5. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1–7.
6. Pan H. LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. Using British 1990 reference data, reanalysed 2009. Version 2.77, 2012.
7. Hird M, Greenough A, Gamsu HR. Gas trapping during high frequency positive pressure ventilation using conventional ventilators. Early Hum Dev. 1990;22:51–6.
8. Radbone L. East of England Perinatal Words. Clinical Guideline: enteral feeding of preterm infants on the neonatal unit. 2013.
9. Torchin H, Ancel PY, Goffinet F, Hascoet JM, Truffert P, Tran D, et al. Placental complications and bronchopulmonary dysplasia: EPIPAGE-2 cohort study. Pediatrics. 2016;137:e20152163.
10. Bose C, Van Marter LJ, Laughon M, O'Shea TM, Allred EN, Karna P, et al. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. Pediatrics. 2009;124:e450–8.
11. Maritz GS, Cock ML, Louey S, Joyce BJ, Albuquerque CA, Harding R. Effects of fetal growth restriction on lung development before and after birth: a morphometric analysis. Pediatr Pulmonol. 2001;32:201–10.
12. Maritz GS, Cock ML, Louey S, Suzuki K, Harding R. Fetal growth restriction has long-term effects on postnatal lung structure in sheep. Pediatr Res. 2004;55:287–95.
13. Frank L, Sosenko IR. Undernutrition as a major contributing factor in the pathogenesis of bronchopulmonary dysplasia. Am Rev Respir Dis. 1988;138:725–9.
14. Bartha JL, Romero-Carmona R, Comino-Delgado R. Inflammatory cytokines in intrauterine growth retardation. Acta Obstet Gynecol Scand. 2003;82:1099–102.
15. McElrath T, Allred EN, Van Marter L, Fichorova RN, Leviton A, ELGAN Study Investigators. Perinatal systemic inflammatory responses of growth-restricted preterm newborns. Acta Paediatr. 2013;102:e439–42.
16. Bardin C, Zelkowitz 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.
17. Grisaru-Granovsky S, Reichman B, Lerner-Geva L, Boyko V, Hammerman C, Samueloff A, et al. Mortality and morbidity in preterm small-for-gestational-age infants: a population-based study. Am J Obst Gynecol. 2012;206:150.e1–7.
18. Griffin IJ, Tancredi DJ, Bertino E, Lee HC, Profit J. Postnatal growth failure in very low birthweight infants born between 2005 and 2012. Arch Dis Child Fetal Neonatal Ed. 2015;101:F50–5.
19. Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000–2013. Pediatrics. 2015;136:e84–92.
20. Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics. 2003;111:986–90.
21. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics. 1999;104:280–9.
22. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? Semin Perinatol. 2003;27:302–10.