Risk Factors and Correlates of Neonatal Growth Velocity in Extremely Low Gestational Age Newborns. The ELGAN Study

Julie Bartholomew^a Camilia R. Martin^b Elizabeth Allred^c Minghua L. Chen^a
Richard A. Ehrenkranz^e Olaf Dammann^{a, d, f} Alan Leviton^c

^aDivision of Newborn Medicine, Floating Hospital for Children at Tufts Medical Center, ^bDepartment of Neonatology Beth Israel Deaconess Medical Center, ^cNeuroepidemiology Unit, Children's Hospital, ^dDepartment of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Mass., and ^eDivision of Perinatal Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, Conn., USA; ^fPerinatal Neuroepidemiology Unit, Hannover Medical School, Hannover, Germany

Key Words

Premature infant · Nutrition · Growth velocity

Abstract

Objectives: To identify maternal and infant characteristics associated with reduced growth velocity (GV) in extremely premature newborns. **Methods:** We evaluated 1,187 infants born between 23 and 27 weeks' gestation at 14 institutions between 2002 and 2004 who survived until day 28 to identify the maternal and infant characteristics associated with a GV and caloric intake in the lowest quartile. **Results:** Newborns in the lowest gestational age and low birth weight categories, as well as those with intrauterine growth restriction, or high SNAP-II received relatively fewer kcal/kg/day than their peers without these risk factors, but were not at increased risk of being in the lowest GV quartile. Newborns with bacteremia, patent ductus arteriosus, retinopathy of prematurity stage 3–5, or pulmonary illness received fewer calories, as did those who received medications or blood transfusions. However, in a multivariable model adjusting for confounders, only ventilator dependence on day 7 (OR 2.2, 95% CI 1.5–3.2), early persistent pulmonary dysfunction (OR 1.8, 95% CI 1.3–2.5), and postnatal exposure to dexa-

methasone (OR 2.8, 95% CI 1.2–6.5) were associated with an increased risk of being in the lowest GV quartile. In this model, low caloric intake was not associated with low GV (OR 1.3, 95% CI 0.9–1.9). **Conclusion:** Variables associated with severe pulmonary disease convey more information about the risk of reduced GV during the first 28 postnatal days than does low caloric intake.

© 2013 S. Karger AG, Basel

Introduction

Many extremely preterm newborns are unable to maintain their birth weight centile at hospital discharge [1]. These infants are at greater risk of neurodevelopmental limitations than their peers who gained more weight [2–4].

Nutritional strategies such as the early introduction of parenteral and enteral feedings and maximizing protein and calorie intake are associated with improved weight gain [5–7]. Nevertheless, some extremely premature newborns do not gain weight as expected even when they receive nutrition within current guidelines [8]. Therefore, neonatal characteristics other than nutrition

are probably important correlates of postnatal weight gain. For example, neonatal illness and treatment-related factors might also contribute to suboptimal weight gain [9].

In this study, we wanted to evaluate to what extent peri- and neonatal characteristics are associated with reduced weight gain while adjusting for potential confounders including the provision of limited calorie intake.

Methods

Sample

The ELGAN (Extremely Low Gestational Age Newborn) Study [10] enrolled women who gave birth before 28 weeks gestation at one of 14 participating institutions. The 1,187 neonates who survived the first 28 postnatal days (79% of the 1,506 recruited infants) and for whom we could calculate growth velocity (GV) and caloric intake are the subjects of this study.

Data Collection

Pregnancy Characteristics

The clinical circumstances that led to preterm delivery were operationally defined using both data from the maternal interview and data abstracted from the medical record.

Placenta Histology

Briefly, infarcts and intervillous fibrin, fetal stem vessel thrombosis, and decidual hemorrhage, fibrin deposition consistent with abruption, syncytial knots and inflammation of the chorionic plate were coded as present or absent.

Newborn Characteristics

Gestational age estimates were based on the dates of embryo retrieval, intrauterine insemination, or fetal ultrasound before the 14th week (62%), followed by fetal ultrasound at 14 or more weeks (29%), then last menstrual period without fetal ultrasound (7%). Intrauterine growth restriction was defined as a birth weight >2 SDs below the expected mean of infants at the same GA in a referent sample [11]. We collected all the data for the first 12 h needed to calculate a SNAP-II™, a validated early illness severity and mortality risk score.

Neonatal Morbidities and Treatment Variables

We recorded the occurrence during the first 28 postnatal days of the following factors: duration of ventilator assistance, pneumothorax, pulmonary interstitial emphysema, pulmonary hemorrhage, early and late bacteremia, diagnosis and treatment of a patent ductus arteriosus (PDA), as well as the receipt of medications and blood products.

ELGANs were classified into three mutually exclusive early respiratory function groups: those with consistently low FiO_2 (an $\text{FiO}_2 < 0.23$ on all days between 3 and 7 days of life and receiving

$\text{FiO}_2 \leq 0.25$ on day 14), those with pulmonary deterioration (PD) (an $\text{FiO}_2 < 0.23$ on any day between 3 and 7 days and receiving $\text{FiO}_2 > 0.25$ on day 14), and those with early and persistent pulmonary dysfunction (EPPD) (an $\text{FiO}_2 \geq 0.23$ on all days between 3 and 7 and receiving $\text{FiO}_2 > 0.25$ on day 14) [12]. Chronic lung disease (CLD) was defined as receipt of supplemental oxygen at 36 weeks' post-menstrual age. Definitions of retinopathy of prematurity (ROP) characteristics were those of the International Committee for Classification of ROP [13].

Growth Velocity

Weights were recorded daily in the first postnatal week, then on days 14, 21 and 28. Because early weight gain is a function of birth weight [14], we chose a measure of GV that divided the daily weight gain by the initial weight. Because ELGANs lose weight during the first postnatal week, we began the GV interval on postnatal day 7 and defined GV as the difference between the day 28 and day 7 weights divided by the weight on day 7, and then divided once again by 21 (the number of days between day 7 and day 28). This number is multiplied by 1,000 to express GV in g/kg/day, so that: $\text{GV}_{7-28} = 1,000 \times [(\text{wt}_{28} - \text{wt}_7)/\text{wt}_7]/21$.

Newborns were separated into four quartiles of GV. The upper bound of the lowest GV quartile was 13.8 g/kg/day, the median was 18.3 g/kg/day, and the upper bound of the third quartile was 22.6 g/kg/day.

Nutritional Practices

Detailed nutritional data collected daily for the first 7 postnatal days then weekly on days 14, 21 and 28 included concentrations, components, additives, and volumes of intravenous solutions, and enteral feedings. Macronutrient content was calculated by multiplying the daily total volume by the macronutrient content on the nutritional label for all formula types and nutritional additives. The specific figures for breast milk calculations were derived from the Ross Neonova system, version 4.5, 1999 (compiled from 'composition of mature and preterm human milk based on values obtained in the literature', Ross Medical Dept.). We used the values for mature milk, since the composition for preterm milk only lasts for approximately 14 postnatal days.

Total kilocalories per day were divided by the birth weight until the birth weight was surpassed, then by the weight on the day the nutritional information was collected. Macronutrient intake was calculated as the mean total kcal/kg/day for 28 days from both parenteral and enteral routes and each newborn was allocated to one of four quartiles of caloric intake based on the calculated mean caloric intake [8].

Statistical Analyses

We evaluated the following two hypotheses, expressed in their null form: (1) ante-, peri- and postnatal characteristics of the newborn are not associated with GV between days 7 and 28 and (2) neonates in the lowest quartile of calories received (per kg/day) have the same risk of being in the lowest quartile for GV regardless of ante-, peri- and postnatal characteristics as their peers who received more calories.

Among newborns with specific pre-, peri-, and neonatal characteristics, we calculated the percentage who received a mean of total kcal/kg/day that was in the lowest quartile, as well as the percent who had a GV in the lowest quartile. If these characteristics were not associated with nutritional intake or GV, one would ex-

Table 1. Percent of infants with the delivery characteristics listed on the left who also were in the lowest quartile of mean total calories (kcal/kg/day) and in the lowest quartile of GV (row percents)

Delivery characteristics		Lowest quartile		n
		total calories [†]	growth velocity [‡]	
Antenatal steroid course	complete	24	25	751
	partial	24	26	309
	none	30	23	123
Pregnancy complication	preterm labor	25	26	530
	pPROM*	24	22	255
	preeclampsia	26	25	154
	abruption	21	30	125
	cervical insufficiency	22	22	73
Duration of labor	0 h	24	21	295
	>0 to ≤12 h	21	25	263
	>12 h	27	27	629
Duration of ruptured membranes	<1 h	25	25	698
	1 to 24 h	23	25	194
	>24 h	24	24	295
Magnesium	none	26	21	379
	tocolysis	24	27	648
	seizure prophylaxis	23	26	149
Cesarean delivery	yes	24	24	789
	no	27	27	398
Fever**	yes	34	39	76
	no	24	24	1,068

[†] Mean of total calories (kcal/kg/day) on days 7, 14, 21, and 28. [‡] $1,000 \times [(\text{weight}_{\text{day 28}} - \text{weight}_{\text{day 7}}) / \text{weight}_{\text{day 7}}] / 21$. * Preterm premature rupture of membranes. ** From before delivery to 48 h after delivery.

pect 25% of neonates with each characteristic to have a nutritional intake or GV in the lowest quartile.

Characteristics associated with an over-representation of neonates in the lowest quartile for GV (>35% where 25% is expected) were entered into multivariable logistic regression models that adjusted for all potential confounders including a hospital stratum variable, and estimated the contribution of limited caloric intake, ante-, peri-, and postnatal characteristics to limited GV. In particular, we created two multivariable logistic regression models of the risk of a GV in the lowest quartile. The first contained only two gestational age categories (i.e. 23–24 and 25–26 weeks), a hospital stratum variable, and a variable for caloric intake in the lowest quartile. The second included these variables plus intercurrent illnesses and their correlates (mechanical ventilation on day 7, EPPD, pneumothorax, pulmonary interstitial emphysema, postnatal receipt of dexamethasone, as well as a sedative). We present the contributions as odds ratios (OR) with 95% confidence intervals (CI).

Table 2. Percent of infants with the characteristics listed on the left who were also in the lowest quartile of mean total calories (kcal/kg/day) and in the lowest quartile of GV among infants (row percents)

Characteristics of the infant		Lowest quartile		n
		total calories [†]	growth velocity [‡]	
Sex	male	26	25	624
	female	27	25	563
Type of gestation	singleton	24	26	798
	multiple	25	23	389
Gestational age, weeks	23–24	43	29	249
	25–26	25	26	551
	27	13	21	387
Birth weight, g*	≤750	37	26	443
	751–1,000	20	26	517
	>1,000	10	20	227
BW Z-score**	<−2	34	23	65
	≥−2, <−1	28	20	154
	≥−1	23	26	968
SNAP-II TM ***	<20	19	22	609
	20–29	28	27	298
	30+	35	30	260

[†] Mean of total calories (kcal/kg/day) on days 7, 14, 21, and 28. [‡] $1,000 \times [(\text{weight}_{\text{day 28}} - \text{weight}_{\text{day 7}}) / \text{weight}_{\text{day 7}}] / 21$. * Birth weight. ** Yudkin et al. standard [11]. *** Score of Neonatal Acute Physiology II [13].

Results

Delivery Characteristics (table 1)

Among all delivery characteristics, only maternal fever was associated with a slightly elevated risk of being in the lowest quartiles of nutrition and GV.

Placenta Characteristics

The percentage of newborns with caloric intake and GV values in the lowest quartile was not over- or under-represented among infants with any of the histologic placenta characteristics we studied (data not shown).

Neonatal Characteristics (table 2)

The percentage of infants whose caloric intake put them in the lowest quartile decreased with increasing gestational age, birth weight, and birth weight Z-score, while it increased with increasing SNAP-IITM. The percentage

Table 3. Percent of infants with the diagnostic and classification entity listed on the left who were also in the lowest quartile of mean total calories (kcal/kg/day) and in the lowest quartile of GV (row percents)

Diagnostic and classification entities		Lowest quartile		n
		total calories [†]	growth velocity [‡]	
Bacteremia, week 1	yes	43	27	75
	no	23	25	1,112
Bacteremia, weeks 2–4	yes	39	25	300
	no	20	25	886
PDA	echo	32	26	624
	clinical	22	25	163
	none	14	23	400
Pneumothorax	yes	49	33	87
	no	23	24	1,100
Pulmonary interstitial emphysema	yes	42	37	186
	no	21	23	1,001
Pulmonary hemorrhage	yes	42	37	43
	no	24	24	1,144
Respiratory group classification	EPPD	31	34	485
	PD	24	18	437
	low FiO ₂	9	17	235
CLD	vent and O ₂	40	26	105
	O ₂ only	29	26	505
	no CLD	18	24	571
Retinopathy of prematurity (stage)	none	16	17	304
	1	14	25	260
	2	27	24	271
	3–5	38	32	345

[†] Mean of total calories (kcal/kg/day) on days 7, 14, 21, and 28.
[‡] $1,000 \times [(\text{weight}_{\text{day 28}} - \text{weight}_{\text{day 7}})/\text{weight}_{\text{day 7}}]/21$.

of infants with GV values in the lowest quartile decreased with increasing gestational age, and increased with increasing SNAP-II™.

Prematurity-Related Illness (table 3)

Neonatal bacteremia, PDA, respiratory illness, and severe ROP were associated with a larger than expected percentage of infants whose caloric intake was in the lowest quartile. Infants with severe ROP and severe respiratory illness had an increased likelihood of being in the lowest GV quartile.

Table 4. Percent of infants with the ventilation characteristics listed on the left who were in the lowest quartile of mean total calories (kcal/kg/day) and in the lowest quartile of GV (row percents)

Time	Mechanical or high-frequency ventilation	Lowest quartile		n
		total calories [†]	growth velocity [‡]	
Day 1	yes	25	26	1,104
	no	16	6	83
Day 7	yes	34	32	715
	no	10	14	471
Day 14	yes	34	30	701
	no	11	18	485
Day 21	yes	37	27	679
	no	8	22	506
Day 28	yes	41	27	575
	no	10	23	607
36 weeks PMA*	yes	40	28	105
	no	23	25	1,076

* Postmenstrual age. [†] Mean of total calories (kcal/kg/day) on days 7, 14, 21, and 28. [‡] $1,000 \times [(\text{weight}_{\text{day 28}} - \text{weight}_{\text{day 7}})/\text{weight}_{\text{day 7}}]/21$.

Ventilation Assistance (table 4)

In light of the associations between severe respiratory illness and low GV, we explored the issue of respiratory care a bit more closely and tabulated infants classified by whether or not they received mechanical or high-frequency ventilation assistance on selected days. While the caloric intake gap between groups widened over the first 4 postnatal weeks, the GV gap tended to become smaller.

Medications and Therapies (table 5)

Almost all pharmacological interventions were associated with an increased risk for being in the lowest quartile of caloric intake, except for methylxanthine exposure, which was associated with a decreased risk. Infants who received dexamethasone were most likely to be in the lowest GV quartile.

Multivariable Analysis (table 6)

In the logistic regression model limited to gestational age categories and a variable for caloric intake in the lowest quartile, only the lowest quartile calories variable was statistically significant (OR 1.5, 95% CI 1.1–2.1). In the

Table 5. Percent of infants with the intervention characteristics listed on the left who were in the lowest quartile of mean total calories (kcal/kg/day) and in the lowest quartile of GV (row percents)

Medications and therapies		Lowest quartile		n
		total calories [†]	growth velocity [‡]	
Surfactant	yes	26	26	1,068
(first week)	no	16	12	119
Methylxanthine	yes	16	22	727
(15+ days)	no	40	30	460
Hydrocortisone	yes	47	31	127
(first 2 weeks)	no	22	24	1,060
Dexamethasone	yes	43	57	28
(first 2 weeks)	no	24	24	1,159
Analgesics	yes	32	28	813
(first 4 weeks)	no	9	18	374
Sedative	yes	46	33	313
(first 4 weeks)	no	17	22	874
PDA treatment*	yes	32	29	729
(first 4 weeks)	no	13	19	458
Transfusion [§]	yes	36	27	681
(in 3–4 weeks)	no	6	22	506

[†] Mean of total calories (kcal/kg/day) on days 7, 14, 21, and 28.
[‡] $1,000 \times [(\text{weight}_{\text{day } 28} - \text{weight}_{\text{day } 7}) / \text{weight}_{\text{day } 7}] / 21$. * Among those with a clinical or echo PDA diagnosis. [§] Packed cells or whole blood.

Table 6. ORs and 95% CIs that variables listed on the left are associated with a GV in the lowest quartile. Estimates are adjusted for the other variables in this table. Estimates are adjusted for the other variables in each of the two logistic regression models. The top model does not include any intercurrent illness, while the bottom model does

	ORs (95% CI)
Without any intercurrent illness	
Gestational age: 23–24 weeks	1.2 (0.8–1.9)
Gestational age: 25–26 weeks	1.2 (0.8–1.7)
Calories in lowest quartile	1.5 (1.1–2.1)
With intercurrent illnesses	
Gestational age: 23–24 weeks	0.8 (0.5–1.3)
Gestational age: 25–26 weeks	1.0 (0.7–1.4)
Mechanical or high-frequency ventilation on day 7	2.2 (1.5–3.2)
EPPD	1.8 (1.3–2.5)
Dexamethasone	2.8 (1.2–6.5)
Sedative	0.9 (0.6–1.3)
Pneumothorax	0.9 (0.5–1.5)
Pulmonary interstitial emphysema	1.3 (0.9–1.9)
Calories in lowest quartile	1.3 (0.9–1.9)
Statistically significant ORs are bold type (p < 0.05).	

model that also included indicators of postnatal illnesses, low caloric intake during the first 28 postnatal days was no longer associated with a GV in the lowest quartile (OR 1.3, 95% CI 0.9–1.9). Infants dependent on ventilator support on postnatal day 7 (OR 2.2, 95% CI 1.5–3.2), those who had EPPD (OR 1.8, 95% CI 1.3–2.5), and those exposed to postnatal dexamethasone (OR 2.8, 95% CI 1.2–6.5) had an increased risk of being in the lowest GV quartile.

Discussion

The first of our major findings is that indicators of breathing difficulties, including ventilator dependence on postnatal day 7, EPPD, and receipt of dexamethasone were each associated with low GV during weeks 2–4. The second major finding is that low GV during that time interval was not associated with caloric intake in the lowest quartile.

Dexamethasone

The relationship between dexamethasone and poor GV is controversial [15, 16]. Because the use of dexamethasone must be viewed as an indicator of the severity

of respiratory dysfunction, the administration of dexamethasone might be an example of confounding by indication [17].

Respiratory Illness

Only one other study found that ventilator-dependent newborns are at increased risk of poor GV [9]. One explanation for a link between ventilation and limited growth invokes systemic inflammation. Mechanically ventilated human newborns [18, 19], adult mice [20] and fetal sheep [21] are more likely than their non-ventilated peers to have systemic inflammation. Another explanation invokes oxidative stress, which is accompanied by systemic inflammation [22].

Ventilator dependence on day 7, but not on days 1, 14 or 28, predicted low GV during weeks 2–4 of life. A likely explanation is that each day of ventilator dependence competes in the multivariable model with each of the other days of ventilator dependence.

Caloric Intake

Neonates who received the lowest amount of calories were not at increased risk of having the most limited weight gain when the multivariable logistic regres-

sion model contained indicators of respiratory dysfunction. This finding leads to the inference that low caloric intake contributes less information about the risk of low weight gain than do indicators of illness severity.

We offer three explanations. First, the sickest newborns are most likely to be fluid overloaded [23]. Second, perhaps total calories are less important than the sources of the calories [8]. Third, their illnesses might limit the absorption and/or utilization of the kilocalories delivered [24].

Modifiable Exposures

Our goal was to find modifiable early risk factors and correlates of poor GV so that newborns with these characteristics would be considered a potential target population for interventions. Of the three characteristics, we identified only dexamethasone exposure can be eliminated easily. Avoiding exposure to mechanical ventilation is possible [25] but difficult, while EPPD is unlikely to be avoided anytime soon.

Our study has several strengths including a large sample size, selection of infants based on gestational age and not birth weight [26], and prospective data collection. Our limitations include an inability to distinguish between causation and association that the sickest infants were more likely to be treated aggressively than others who were not quite so sick, making our study prone to

confounding by indication [17], and reliance on GV as a measure of adequate nutrition. Ideally, more precise measures of nutrition are needed.

Conclusions

Among ELGANs, indicators of early pulmonary illness severity, including receipt of dexamethasone, but not low caloric intake, are associated with an increased risk for GV below the 25th percentile during postnatal weeks 2–4.

Acknowledgements

This study was supported by NIH (5U01NS040069-05 and P30-HD-18655). The authors gratefully acknowledge the contributions of their subjects and their families, as well as those of their colleagues, who are identified below: Bhavesh Shah, Karen Christianson, Colleen Hallisey, Caitlin Hurley, Miren Creixell, Linda J. Van Marter, Kathleen Lee, Anne McGovern, Jill Gambardella, Susan Ursprung, Ruth Blomquist, Robert Insoft, Jennifer G. Wilson, Maureen Pimental, Cynthia Cole, John Fiascone, Janet Madden, Ellen Nysten, Anne Furey, Francis Bednarek, Mary Naples, Beth Powers, Joanne Williams, Elaine Romano, T. Michael O'Shea, Debbie Gordon, Teresa Harold, Gail Hounsell, Debbie Hiatt, Stephen Engelke, Sherry Moseley, Linda Pare, Donna Smart, Joan Wilson, Carl Bose, Gennie Bose, Janice Wereszczak, Mariel Portenga, Dinah Sutton, Padmani Karna, Carolyn Solomon, Michael D. Schreiber, Grace Yoon, Daniel Batton, and Beth Kring.

References

- 1 Ehrenkranz RA, Younes N, Lemons JA, et al: Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics* 1999;104:280–289.
- 2 Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH: Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. *J Pediatr* 2003; 143:163–170.
- 3 Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wraage LA, Poole WK: Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006;117:1253–1261.
- 4 Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R: Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. *Pediatrics* 2006;118:1078–1086.
- 5 Olsen IE, Richardson DK, Schmid CH, Ausman LM, Dwyer JT: Intersite differences in weight growth velocity of extremely premature infants. *Pediatrics* 2002;110:1125–1132.
- 6 Wilson DC, Cairns P, Halliday HL, Reid M, McClure G, Dodge JA: Randomised controlled trial of an aggressive nutritional regimen in sick very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 1997; 77:F4–F11.
- 7 Pointdexter B: Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcomes. *J Pediatr* 2006; 148:6.
- 8 Martin CR, Brown YF, Ehrenkranz RA, et al: Nutritional practices and growth velocity in the first month of life in extremely premature infants. *Pediatrics* 2009;124:649–657.
- 9 Loui A, Tsaliakaki E, Maier K, Walch E, Karmarianakis Y, Obladen M: Growth in high risk infants <1,500 g birthweight during the first 5 weeks. *Early Hum Dev* 2008;84:645–650.
- 10 O'Shea TM, Allred EN, Dammann O, et al: The ELGAN Study of the brain and related disorders in extremely low gestational age newborns. *Early Hum Dev* 2009;85:719–725.
- 11 Yudkin PL, Aboualfa M, Eyre JA, Redman CW, Wilkinson AR: New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. *Early Hum Dev* 1987;15: 45–52.
- 12 Laughon M, Allred EN, Bose C, et al: Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. *Pediatrics* 2009;123:1124–1131.
- 13 The Committee for the Classification of Retinopathy of Prematurity: An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130–1134.
- 14 Bloom BT, Mulligan J, Arnold C, et al: Improving growth of very low birth weight infants in the first 28 days. *Pediatrics* 2003;112: 8–14.

- 15 Gibson AT, Pearce RG, Wales JK: Growth retardation after dexamethasone administration: assessment by knemometry. *Arch Dis Child* 1993;69:505–509.
- 16 Doyle LW, Ehrenkranz RA, Halliday HL: Dexamethasone treatment after the first week of life for bronchopulmonary dysplasia in preterm infants: a systematic review. *Neonatology* 2010;98:289–296.
- 17 Bosco JL, Silliman RA, Thwin SS, et al: A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010;63:64–74.
- 18 Bohrer B, Silveira RC, Neto EC, Procianny RS: Mechanical ventilation of newborns infant changes in plasma pro- and anti-inflammatory cytokines. *J Pediatr* 2010;156:16–19.
- 19 Bose CL, Laughon MM, Allred EN, et al: Systemic inflammation associated with mechanical ventilation among extremely preterm infants. *Cytokine* 2013;61:315–322.
- 20 Walker MG, Yao LJ, Patterson EK, et al: The effect of tidal volume on systemic inflammation in acid-induced lung injury. *Respiration* 2011;81:333–342.
- 21 Hillman NH, Polglase GR, Pillow JJ, Saito M, Kallapur SG, Jobe AH: Inflammation and lung maturation from stretch injury in preterm fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2011;300:L232–L241.
- 22 Vento M, Moro M, Escrig R, et al: Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics* 2009;124:e439–e449.
- 23 Oh W: Renal function and fluid therapy in high risk infants. *Biol Neonate* 1988;53:230–236.
- 24 Shields B, Wacogne I, Wright CM: Weight faltering and failure to thrive in infancy and early childhood. *BMJ* 2012;345:e5931.
- 25 Gopel W, Kribs A, Ziegler A, et al: Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet* 2011;378:1627–1634.
- 26 Arnold CC, Kramer MS, Hobbs CA, McLean FH, Usher RH: Very low birth weight: a problematic cohort for epidemiologic studies of very small or immature neonates. *Am J Epidemiol* 1991;134:604–613.