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ORIGINAL ARTICLE

Heart rate characteristics and neurodevelopmental outcome in very low birth weight infants

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Background: Sepsis in very low birth weight (VLBW) infants has been associated with an increased risk of adverse developmental outcome. We have identified abnormal heart rate characteristics (HRCs) that are predictive of impending sepsis, and we have developed a summary measure of an infant's abnormal HRCs during the neonatal hospitalization that we refer to as the cumulative HRC score (cHRC).

Objective: In this study, we tested the hypothesis that increasing cHRC is associated with an increasing risk of adverse neurodevelopmental outcome in VLBW infants.

Method: Data were collected on 65 VLBW infants whose HRCs were monitored while in the neonatal intensive care unit and who were examined at 12 to 18 months adjusted age. Using the Bayley Scale of Infant Development-II, we identified delays in early cognitive function (i.e., Mental Developmental Index <70) and psychomotor development (i.e., Psychomotor Developmental Index <70). Cerebral palsy (CP) was diagnosed using a standard neurological examination.

Result: Increasing cHRC score was associated with an increased risk of CP (odds ratio per 1 standard deviation increase in cHRC: 2.6, 95% confidence limits: 1.42, 5.1) and delayed early cognitive development [odds ratio: 2.3 (1.3; 4.3)]. These associations remain statistically significant when adjusted for major cranial ultrasound abnormality. There was an association of increasing cHRC and delayed psychomotor development, which did not reach statistical significance [odds ratio: 1.7 (1.0, 3.0)].

Conclusion: Among VLBW infants, the cumulative frequency of abnormal HRCs, which can be assessed non-invasively in the neonatal intensive care unit, is associated with an increased risk of adverse neurodevelopmental outcome.

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Introduction

Very low birth weight (VLBW) infants are at a high risk for sepsis[1] and have an increased incidence of cerebral palsy (CP) and developmental delay compared with full term infants.[2,3] Recent studies indicate that sepsis and the systemic inflammatory response syndrome (SIRS) are associated with an increased risk for developmental impairments in infants born prematurely.[4–6]

We have reported that certain heart rate characteristics (HRCs), specifically, transient decelerations, decreased variability, and a lack of accelerations, can be used to identify infants who are at increased risk for developing either sepsis or systemic inflammatory response.[7–9] A summation of an infant's abnormal HRC during neonatal hospitalization, referred to as the cumulative HRC (cHRC) index, is predictive of mortality.[10] In the current study, we analyzed association between cHRC during the neonatal hospitalization and neurodevelopmental outcome between 12 and 18 months corrected age. Our objective was to determine whether an elevated cHRC is associated with adverse neurodevelopmental outcome at 12 to 18 months corrected age.

Methods

This study was approved by the Wake Forest University Health Sciences Institutional Review Board.

Study participants

Inclusion criteria for this study were as follows: (1) birth weight <1500 g; (2) admitted to the Wake Forest University Baptist Medical Center Intensive Care Nursery between 1999 and 2001; (3) evaluated at 12 months adjusted age at the Wake Forest University Development Evaluation Clinic; (4) at least 12, 6-h

epochs of HRC monitoring available for analysis; (5) no major congenital anomaly. The study was approved by the Wake Forest University Baptist Medical Center Institutional Review Board with a waiver of the requirement for informed consent.

Measurements

Collection of HRCs data

Heart rate data were collected non-invasively from the bedside monitors used in routine care of infants in the Wake Forest University Baptist Medical Center Intensive Care Nursery. Data were collected continuously 24 h a day without selection of epochs relevant to sleep, feeding, clinical status, or any other factors. Briefly, an analog electrocardiographic signal is obtained from the defib-sync output port of the bedside monitor. This signal is digitized at 4 kHz by a microcomputer at the bedside. The data are high-pass filtered, and QRS complexes are identified using amplitude and duration criteria to generate sets of RR intervals. These sets of intervals are used to generate HRC parameters including standard deviation, sample asymmetry, and sample entropy analyses. These parameters are used as inputs to a predictive model algorithm using a multivariable logistic regression that was developed at the University of Virginia and externally validated at Wake Forest University. The output of the model is divided by the average risk of sepsis and presented as the fold-increase in risk of sepsis in the net 24 h.

Calculation of HRCs

Sample asymmetry. Quadratic 'risk-analysis' functions are calculated using raw data. Given a series of 4096 RR intervals x_1, x_2, … x_{4096} with median $= m$, we compute $r_1(x_i) = r(x_i)$ if $x_i < m$; 0 otherwise, and $r_2(x_i) = r(x_i)$ if $x_i > m$; 0 otherwise. The Left (R_1) and Right (R_2) HRC risks are:

$$R_1 = \frac{1}{4096} \sum_{i=1}^{4096} r_1(x_i)^2$$

and

$$R_2 = \frac{1}{4096} \sum_{i=1}^{4096} r_2(x_i)^2$$

respectively.

The parameters of interest are R_1, which relates to the number and extent of HR accelerations, R_2, which similarly reports on decelerations, and the ratio R_2/R_1, which we have called the sample asymmetry.[11]

Sample entropy. Sample entropy (SampEn) is calculated with $m = 3$, $r = 0.2$ as described[12] using filtered, normalized data. In this context, reduced sample entropy occurs when both reduced variability and transient decelerations are present.[13]

Predictive multi-variable statistical models. These have the form of regression expressions of the form:

$$\text{prob}(Y = 1) = \frac{\exp(\log\text{it}(Y = 1))}{1 + \exp(\log\text{it}(Y = 1))}$$

where:

$$\log\text{it}(Y = 1) = \beta_0 + \beta_1 \text{HRC}_1 + \beta_2 \text{HRC}_2 + \ldots + \beta_m \text{HRC}_m$$

where HRC_m are HRCs of interest.

Calculation of cHRC

The infant's hospital stay was divided into 6 h epochs. For each 6 h epoch, the infant was given a demographic index, calculated from a logistic regression model containing the variables for gestational age, birth weight, and days of age.[7] The infant was also given a HRC index value for each 6 h epoch, calculated from a different logistic regression model using the HRCs as input variables. The probability of sepsis or SIRS over the next 24 h of the infant's life was the outcome variable used in both of these logistic regression models. Therefore, the demographic index is the probability that sepsis or systemic inflammatory response will occur within the next 24 h as predicted only by the demographic variables and the HRC index is the probability that sepsis or SIRS will occur within the next 24 h as predicted by the HRCs. The cHRC is calculated by subtracting the demographic index from the HRC index for each epoch, and then summing up all the epochs of the infant's stay.[10]

$$\text{cHRC} = \sum [(\text{HRC index}) - (\text{Demographic index})]$$

Therefore, the cHRC gives an overall picture of whether the infant clinically did better or worse than expected for the average infant based solely on knowing the birth weight and gestational age. If the infant had a benign hospital course and did better than expected, then the majority of the HRC index values would be low and the cHRC would be less than zero. If the infant did poorly, with multiple episodes of sepsis or SIRS, then the majority of the HRC index values would be high and the cHRC would be greater than zero. If the infant had a typical hospital course, then the cHRC would be close to zero.

Patient characteristics

Data about birth weight, gestational age, gender, race, chronic lung disease, and cranial ultrasound abnormalities were obtained from an electronic database maintained at our follow-up clinic. The data were abstracted from medical records by a study coordinator who was not aware of the study hypothesis or the infants' cHRC score. Sepsis was defined as a positive blood culture treated with at least 7 days of antibiotics. Small for gestational age was defined as birth weight less than the 10th percentile for gestational age, based on data reported by Alexander *et al*.[14]

Chronic lung disease was defined as the need for supplemental oxygen at 36 weeks postmenstrual age.[15] Major cranial ultrasound abnormalities were defined as any of the following: (1) periventricular echodensity located ipsilateral to a presumed intraventricular hemorrhage (i.e., abnormal echodensity in the ventricle); (2) posthemorrhagic hydrocephalus requiring neurosurgical intervention; (3) moderate or severe ventricular enlargement on a 'late' (performed after the first month of life) ultrasound; or (4) periventricular echolucency.[16]

Developmental outcomes

Follow-up data were obtained at 12 ($n = 58$) or 18 ($n = 7$) months adjusted age at the Wake Forest University Development Evaluation Clinic. Children were classified as having CP or not by a standardized neurological examination performed by physicians who were aware of the patient's medical history, but not aware of the cHRC score. The Bayley Scales of Infant Development-Second Edition (BSID-II)[17] was administered by child psychologists who were not aware of the child's medical history. After testing was completed, the psychologists learned of the child's gestational age at birth to derive the BSID-II scores adjusted for gestational age.

CP was defined as a non-progressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture resulting in impaired motor function.[18] Delayed early cognitive development was defined as a BSID-II Mental Development Index (MDI) <70; delayed psychomotor development was defined as a Psychomotor Development Index (PDI) <70. We used the term neurodevelopmental impairment to refer to a composite outcome of either CP or a BSID MDI or PDI <70.

Data analysis

We analyzed associations between cHRC and developmental outcome in several ways: (1) correlations between cHRC and MDI and cHRC and PDI were analyzed using Spearman rank correlation coefficients; (2) infants were classified into cHRC quartiles for each of the dichotomous outcomes of interest (i.e., CP, delayed early cognitive and psychomotor development, a composite outcome of CP or delayed early cognitive development) and the resulting 2×4 contingency tables were analyzed using the Cochran-Armitage test for trend.[19] (3) Logistic models were used to estimate the odds ratios for the association of cHRC, entered as a continuous variable, and the dichotomous outcomes of interest. To compare groups of infants with and without each outcome of interest, we used the Wilcoxon rank sum test for continuous variables and the χ^2 or Fisher's exact test for categorical variables.

Multivariate analysis was performed using logistic regression. Only variables that had a *P*-value <0.1 in the univariate analysis were included in the logistic regression model. Variables with the highest *P*-value were eliminated one at a time using stepwise elimination until all variables within the model had adjusted *P*-values <0.1. All statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC.)

Results

The attributes of these infants are summarized in Table 1. The median cHRC was 4.0, and the range was −4.9 to 43.5. cHRC was inversely correlated with both MDI (Spearman's rho = −0.29, $P = 0.02$) and PDI (Spearman's rho = −0.39, $P = 0.001$; data not shown). The Cochran-Armitage test for trend showed a statistically significant linear trend between the quartiles for CP, MDI <70, and the composite outcome of CP or MDI <70 (all *P*-values <0.05; data not shown). cHRC was higher among infants with sepsis ($P = 0.002$), but significant associations were not found between sepsis and any of the developmental outcomes of interest (all *P*-values >0.1; data not shown).

Table 2 summarizes associations between infant characteristics and the developmental outcomes of interest. At significance level of 0.1, cHRC and major cranial ultrasound abnormality were associated with each of the developmental outcomes that we studied. Gestational age was associated with an increased risk of CP, MDI <70, and birth weight was associated with MDI <70. Chronic lung disease was associated with MDI <70, and necrotizing enterocolitis was associated with PDI <70. Non-white race was associated with an increased risk of CP.

Table 1 Characteristics and outcomes of study infants

Characteristic/outcome	*VLBW infants (n = 65)*
Gestational age (weeks)[a]	26 (22–33)
Birth weight (g)[a]	792 (406–1470)
Small for gestational age	7 (11)
Race	
White	37 (57)
Non-white	28 (43)
Female gender	36 (55)
Sepsis	46 (71)
Necrotizing enterocolitis	10 (15)
Chronic lung disease	34 (52)
Major ultrasound abnormality	17 (26)
cHRC[a]	4.0 (−4.9 to 43.5)
Cerebral palsy	10 (16)[b]
MDI <70	11 (17)
PDI <70	27 (42)
NDI	16 (25)

Data are number of infants (percentage in parenthesis) except where noted.
[a]Data are median (range in parenthesis).
[b]One infant did not undergo neurological examination at follow-up.
Abbreviations: cHRC, cumulative heart rate characteristics index; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; NDI, neurodevelopmental impairment.

Table 2 Characteristics of VLBW infants with and without developmental impairments

Characteristic	*Cerebral palsy*		*MDI <70*		*PDI <70*	
	Absent (n = *54*)	*Present* (n = *10*)	*Absent* (n = *54*)	*Present* (n = *11*)	*Absent* (n = *38*)	*Present* (n = *27*)
Gestational age (weeks)	27 (23–31)	25 (22–33)*	27 (22–33)	25 (23–29)*	26.5 (22–31)	26 (23–33)
Birth weight (g)	798 (440–1470)	725 (406–1470)	814 (440–1470)	650 (406–1439)*	798 (440–1470)	790 (406–1470)
Small for gestational age	5 (9)	2 (20)	5 (9)	2 (18)	2 (5)	5 (19)
Race						
White	34 (63)	3 (30)*	31 (57)	6 (55)	21 (55)	16 (59)
Non-white	20 (37)	7 (70)	23 (43)	5 (45)	17 (45)	11 (41)
Female gender	31 (57)	4 (40)	29 (54)	7 (64)	21 (55)	15 (56)
Sepsis	37 (69)	8 (80)	37 (69)	9 (82)	24 (63)	22 (81)
Necrotizing enterocolitis	8 (15)	2 (20)	8 (15)	2 (18)	3 (8)	7 (26)*
Chronic lung disease	27 (50)	6 (60)	24 (44)	10 (91)*	18 (47)	16 (59)
Major Ultrasound abnormality	10 (19)	7 (70)*	11 (20)	6 (55)*	6 (16)	11 (41)*
cHRC	3.76 (−4.91 to 41.08)	18.14 (−1.61 to 43.48)*	−2.31 (−4.91 to 33.60)	9.20 (−1.61 to 43.48)*	2.05 (−4.91 to 22.06)	5.53 (−1.61 to 43.48)*

Data are medians (range in parenthesis) or number of infants (percentage in parenthesis). *$P<0.1$.
Abbreviation: cHRC, cumulative heart rate characteristics index.

Table 3 Multivariate analysis

Outcome	*OR (95% CI)*	P-*value*	*Adjusted OR (95% CI)*	P-*value*
Cerebral palsy	2.6 (1.4–5.1)	0.004	2.3 (1.2, 4.7)[a]	0.02
MDI <70	2.3 (1.3–4.3)	0.007	2.1 (1.0, 4.2)[b]	0.04
PDI <70	1.7 (1.0–3.0)	0.06	1.5 (0.9, 2.7)[a]	0.1
NDI	3.3 (1.6–7.0)	0.002	3.0 (1.4, 6.6)[a]	0.005

Odds ratios and 95% confidence intervals for each 10 unit increase in cHRC.
[a]OR adjusted for head ultrasound results.
[b]OR adjusted for head ultrasound results and chronic lung disease.
Abbreviations: cHRC, cumulative heart rate characteristics index; OR, odds ratio; CI, confidence interval; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index; NDI, neurodevelopmental impairment.

In multivariate analyses in which the outcomes of interest were CP, PDI <70, and the composite outcome of CP or delayed early cognitive development, only cHRC and major cranial ultrasound abnormalities were retained when variables were eliminated in a stepwise fashion using $\alpha < 0.1$ as the criteria for remaining in the model. In analyses in which the outcome of interest was delayed MDI <70, chronic lung disease was also significant at $P<0.1$. Unadjusted and adjusted odds ratios for a one standard deviation increase in cHRC are presented in Table 3.

Discussion

In a sample of VLBW infants, we found that cHRC is correlated with scores on the BSID-II and that the risk of CP increases with increasing cHRC. These associations were attenuated only slightly when adjusted for the presence of major abnormalities on cranial ultrasound. Thus, cHRC is associated not only with mortality, as we have described earlier, but also with developmental impairments among VLBW. As would be expected, we found higher cHRC values among infants who were diagnosed with sepsis. Although we did not collect data about the occurrence of culture-negative sepsis, our prior studies indicate that the HRCs that influence cHRC are found in infants with both culture-positive and culture-negative sepsis.[9]

The HRCs that determine cHRC have been associated with impending neonatal sepsis, an event that may initiate a systemic inflammatory response (SIRS), including increased levels of blood cytokines.[20] A growing body of evidence suggests a link between fetal and neonatal inflammation, increased blood levels of inflammatory cytokines, and subsequent neurodevelopmental impairments.[4–6,21] Although our results demonstrate an association between cHRC and neurodevelopmental outcome, our findings are in agreement with Vohr *et al*.,[22] in that we did not find an association between culture proven sepsis and adverse neurodevelopmental outcome. Thus, elevated cHRC may be indicative of not only culture proven sepsis, but other initiators of inflammation, such as SIRS with negative cultures and necrotizing enterocolitis.

White matter damage, as indicated by persistent ventricular enlargement or cerebral echolucency on cranial ultrasound,[23] is probably the strongest single predictor of CP[24,25] and delayed early cognitive functioning[22,26] among VLBW infants. Experiments in animal models[4,27] and observational studies in humans[28] suggest that initiators of fetal and neonatal inflammation are associated with neonatal white matter damage. Increased levels of inflammatory cytokines have been detected in the amniotic fluid of infants who subsequently developed periventricular white matter

damage.[29] The HRC index rises with sepsis,[9,30,31] when blood levels of inflammatory cytokines would be expected to increase.[20] Thus, an elevated cHRC score may be reporting on exposure to one of the putative causes of brain damage in preterm infants.

Despite its usefulness in identifying brain damage, white matter as seen on cranial ultrasound has been referred to as the 'tip of the iceberg'[32] because ultrasound fails to detect white matter damage in a substantial proportion of affected infants.[33,34] This may explain why almost 25% of extremely low birth weight infants with developmental impairment have normal cranial ultrasound.[35] The current study suggests that in addition to its potential as a means of earlier identification of impending sepsis,[7,9,31] HRC monitoring might provide prognostic information that is to some degree complementary to that provided by cranial ultrasound.[36,37] Somewhat similar approaches were used by Mattia and deRegnier,[38] who found that the summation of the Severity of Neonatal Acute Physiology scores was predictive of lower MDI and PDI scores at 2 to 3 years of age, and Broitman *et al*.,[39] who found that a multivariate index derived from clinical data were a better predictor of developmental impairment than cranial ultrasound.[39]

The association of cHRC with delayed psychomotor development was weaker than that between cHRC and the other neurodevelopmental outcomes that we studied. It is possible that the reliability of our assessments of psychomotor development at 12 to 18 months adjusted age was lower than that of our assessments of early cognitive development (with the MDI). A second possibility is that the risk factor profile differs for MDI <70 and PDI <70. For example, major cranial ultrasound abnormalities, chronic lung disease and necrotizing enterocolitis are associated more strongly with PDI <70 than with MDI <70.[22,40]

The specific HRCs that we studied here have not been previously analyzed in relation to neurodevelopmental outcomes. However, others have studied the maturation of heart rate variability, which is one of the variables that influences cHRC. In preterm infants, greater heart rate variability at 40 weeks postmenstrual age was found to be predictive of higher Bayley MDI,[41] and the rate maturation of heart rate variability between 33 and 35 weeks postmenstrual age has been correlated with better behavior regulation at 3 years[42] and greater social competency at 6 to 9 years.[43]

We should note that there are several limitations in our study; most important is our relatively small convenience sample. All of these infants were transported to a tertiary hospital and would, therefore, be at high risk of developmental impairments. For example, the prevalence of CP (16%) described here is higher than that reported from population-based studies.[18,44] Second, this is a retrospective analysis, which likely limited the validity of data about potential confounders, such as cranial ultrasound findings, limiting our ability to adjust for these confounders. We also had limited information about socioeconomic status, which is associated with performance on the BSID.[22] Third, although the physicians who performed the neurological assessments were not aware of infants' cHRC, they were aware of the infant's medical history, which could have led to ascertainment bias if these examiners suspected an association between events that increase cHRC (such as neonatal sepsis) and subsequent developmental impairments. Finally, examinations at 12 to 18 months adjusted age are somewhat limited in their sensitivity for identification of CP[45] and delayed early cognitive functioning ability,[46] which may have resulted in misclassification of infants with respect to the presence of developmental impairment. Before applying our findings to the clinical care of patients, replication is needed in a larger, and more representative sample of high-risk infants, with data about potential confounders prospectively collected.

Despite these limitations, the results of our study support the need for larger analyses of the relationship of neonatal cHRC score to neurodevelopmental outcome. If an association of cHRC and outcome is confirmed in larger studies, more study of the antecedents of cHRC would be warranted. Study is needed also of the relationship between HR variability and known antecedents of poor long-term outcome, such as necrotizing enterocolitis[47] and chronic lung disease.[48] Research into the possible mechanisms linking HRCs and developmental outcome should include assessment of inflammatory cytokines and other biomarkers of inflammation.[49]

The data from which the cHRC is derived can be obtained non-invasively with a commercially available device, but modification of the software programming in this device would be needed to automate computation of the cHRC. The clinical utility of continuous HRCs monitoring is currently under study (ClinicalTrials.gov Identifier: NCT00307333). At the present time, we can only speculate as to the clinical utility of cHRC. cHRC might add to the predictive information conveyed by cranial ultrasound findings[24,37] and clinical data.[39] Improved prediction of neurodevelopment impairment could allow clinicians to target infants at highest risk so that early intervention could be initiated, and outcome improved.[50]

Conflict of interest

Medical Predictive Science Corporation of Charlottesville, Virginia, has a license to market technology related to HRCs monitoring of newborn infants, and supplied partial funding for this study and aided in collection of the data. They played no role in the study design, analysis and interpretation of data, writing of the report, or the decision to submit the paper for publication. Drs Moorman and Lake have an equity share in this company.

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References

1 Fanaroff AA, Stoll B, Wright LL, Carlo WA, Ehrenkranz R, Stark A *et al.* Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol* 2007; **147**: e1–e8.

2 Drummond PM, Colver AF. Analysis by gestational age of cerebral palsy in singleton births in north-east England 1970-94. *Paediatr Perinat Epidemiol* 2002; **16**(2): 172–180.

3 Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. *Pediatrics* 2002; **110**(6): 1220–1225.

4 Dammann O, Leviton A. Inflammatory brain damage in preterm newborns - dry numbers, wet lab, and causal inferences. *Early Hum Dev* 2004; **79**(1): 1–15.

5 Wu YW. Systematic review of chorioamnionitis and cerebral palsy. *Ment Retard Dev Disabil Res Rev* 2002; **8**(1): 25–29.

6 O'Shea TM. Cerebral palsy in very preterm infants: new epidemiological insights. *Ment Retard Dev Disabil Res Rev* 2002; **8**(3): 135–145.

7 Griffin MP, O'Shea TM, Bissonette EA, Harrell FE, Lake DE, Moorman JR. Abnormal heart rate characteristics preceding neonatal sepsis and sepsis-like illness. *Pediatr Res* 2003; **53**(6): 920–926.

8 Griffin MP, Lake DE, Bissonette EA, Harrell FE, O'Shea TM, Moorman JR. Heart rate characteristics: Novel physiomarkers to predict neonatal infection and death. *Pediatrics* 2005; **116**(5): 1070–1074.

9 Griffin MP, Moorman JR. Toward the early diagnosis of neonatal sepsis and sepsis-like illness using novel heart rate analysis. *Pediatrics* 2001; **107**(1): 97–104.

10 Griffin MP, O'Shea TM, Bissonette EA, Harrell FE, Lake DE, Moorman JR. Abnormal heart rate characteristics are associated with neonatal mortality. *Pediatr Res* 2004; **55**(5): 782–788.

11 Kovatchev BP, Farhy LS, Cao HQ, Griffin P, Lake DE, Moorman JR. Sample asymmetry analysis of heart rate characteristics with application to neonatal sepsis and systemic inflammatory response syndrome. *Pediatr Res* 2003; **54**(6): 892–898.

12 Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol* 2000; **278**(6): H2039–H2049.

13 Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. *Am J Physiol Regul Integr Comp Physiol* 2002; **283**(3): R789–R797.

14 Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol* 1996; **87**(2): 163–168.

15 Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. *Pediatrics* 1988; **82**(4): 527–532.

16 Stewart AL, Reynolds EO, Hope PL, Hamilton PA, Baudin J, Costello AM *et al.* Probability of neurodevelopmental disorders estimated from ultrasound appearance of brains of very preterm infants. *Dev Med Child Neurol* 1987; **29**(1): 3–11.

17 Bayley N. *Bayley Scales of Infant Development-Second Edition*. 2nd edn Psychological Corporation, San Antonio, 1993.

18 O'Shea TM, Preisser JS, Klinepeter KL, Dillard RG. Trends in mortality and cerebral palsy in a geographically based cohort of very low birth weight neonates born between 1982 to 1994. *Pediatrics* 1998; **101**(4 Pt 1): 642–647.

19 Armitage P. Test for linear trend in proportions and frequencies. *Biometrics* 1955; **11**(375): 386.

20 Malik A, Hui CPS, Pennie RA, Kirpalani H. Beyond the complete blood cell count and C-reactive protein—a systematic review of modern diagnostic tests for neonatal sepsis. *Arch Pediatr Adolesc Med* 2003; **157**(6): 511–516.

21 Dammann O, Leviton A. The role of the fetus in perinatal infection and neonatal brain injury. *Curr Opin Pediatr* 2000; **12**(2): 99–104.

22 Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ *et al.* Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994. *Pediatrics* 2000; **105**(6): 1216–1226.

23 Paneth N. Classifying brain damage in preterm infants. *J Pediatr* 1999; **134**(5): 527–529.

24 de Vries LS, Van Haastert ILC, Rademaker KJ, Koopman C, Groenedaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. *J Pediatr* 2004; **144**(6): 815–820.

25 Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics* 1995; **95**(2): 249–254.

26 Whitaker A, Johnson J, Sebris S, Pinto J, Wasserman G, Kairam R *et al.* Neonatal cranial ultrasound abnormalities—association with developmental delay at age one in low-birth-weight infants. *J Dev Behav Pediatr* 1990; **11**(5): 253–260.

27 Hagberg H, Peebles D, Mallard C. Models of white matter injury: comparison of infectious, hypoxic-ischemic, and excitotoxic insults. *Ment Retard Dev Disabil Res Rev* 2002; **8**(1): 30–38.

28 Wu YW, Colford JM. Chorioamnionitis as a risk factor for cerebral palsy—a meta-analysis. *JAMA* 2000; **284**(11): 1417–1424.

29 Yoon BH, Jun JK, Romero R, Park KH, Gomez R, Choi JH *et al.* Amniotic fluid inflammatory cytokines (interleukin-6, interleukin- 1beta, and tumor necrosis factor-alpha), neonatal brain white matter lesions, and cerebral palsy. *Am J Obstet Gynecol* 1997; **177**(1): 19–26.

30 Griffin MP, Lake DE, O'Shea TM, Moorman JR. Heart rate characteristics and clinical signs in neonatal sepsis. *Pediatr Res* 2007; **61**(2): 222–227.

31 Griffin MP, Lake DE, Moorman JR. Heart rate characteristics and laboratory tests in neonatal sepsis. *Pediatrics* 2005; **115**(4): 937–941.

32 Leviton A, Gilles F. Ventriculomegaly, delayed myelination, white matter hypoplasia, and 'periventricular' leukomalacia: how are they related? *Pediatr Neurol* 1996; **15**: 127–136.

33 Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan F, Azzopardi D *et al.* Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. *Pediatrics* 2001; **107**(4): 719–727.

34 Inder TE, Anderson NJ, Spencer C, Wells S, Volpe JJ. White matter injury in the premature infant: a comparison between serial cranial sonographic and MR findings at term. *Am J Neuroradiol* 2003; **24**(5): 805–809.

35 Laptook AR, O'Shea TM, Shankaran S, Bhaskar B, NICHD Neonatal Network. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics* 2005; **115**: 673–680.

36 Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA *et al.* Practice parameter: neuroimaging of the neonate—report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002; **58**(12): 1726–1738.

37 O'Shea TM, Counsell SJ, Bartels DB, Dammann O. Magnetic resonance and ultrasound brain imaging in preterm infants. *Early Hum Dev* 2005; **81**(3): 263–271.

38 Mattia FR, deRegnier RA. Chronic physiologic instability is associated with neurodevelopmental morbidity at one and two years in extremely premature infants. *Pediatrics* 1998; **102**(3): E35.

39 Broitman E, Namasivayam A, Higgins RD, Vohr BR, Das A, Bhaskar B *et al.* Clinical data predict neurodevelopmental outcome better than head ultrasound in extremely low birth weight infants. *J Pediatr* 2007; **151**(5): 500–505.

40 O'Shea TM, Kuban KCK, Allred EN, Paneth N, Pagano M, Dammann O *et al.* Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. *Pediatrics* 2008; **122**(3): E662–E669.

41 Fox NA, Porges SW. The relation between neonatal heart period patterns and developmental outcome. *Child Dev* 1985; **56**(1): 28–37.
42 Doussard-Roosevelt JA, Porges SW, Scanlon JW, Alemi B, Scanlon KB. Vagal regulation of heart rate in the prediction of developmental outcome for very low birth weight preterm infants. *Child Dev* 1997; **68**(2): 173–186.
43 Doussard-Roosevelt JA, McClenny BD, Porges SW. Neonatal cardiac vagal tone and school-age developmental outcome in very low birth weight infants. *Dev Psychobiol* 2001; **38**(1): 56–66.
44 Cummins SK, Nelson KB, Grether JK, Velie EM. Cerebral palsy in four northern California counties, births 1983 through 1985. *J Pediatr* 1993; **123**(2): 230–237.
45 Nelson KB, Ellenberg JH. Children who 'outgrew' cerebral palsy. *Pediatrics* 1982; **69**: 529–536.
46 O'Shea TM, Goldstein DJ. Follow-up data—their use in evidence-based decision-making. *Clin Perinatol* 2003; **30**(2): 217–250.
47 Hintz SR, Kendrick DE, Stoll BJ, Vohr BR, Fanaroff AA, Donovan EF *et al.* Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. *Pediatrics* 2005; **115**(3): 696–703.
48 Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA *et al.* Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005; **116**(6): 1353–1360.
49 Dammann O, O'Shea TM. Cytokines and perinatal brain damage. *Clin Perinatol* 2008; **35**(4): 643–663.
50 Spittle AJ, Orton J, Doyle LW, Boyd R. Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants. *Cochrane Database Syst Rev* 2007; **2**: CD005495.