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Abstract

Objectives: This study is an investigation of differences in regulatory problems (RP; crying, sleeping, feeding) expressed by infants born very preterm (VP; <32 weeks gestation) or with very low birth weight (VLBW; <1500 grams) and infants born at full term (FT) during the first 18 months of life. It investigates the prevalence of single and multiple RPs, their persistence and how early in infancy RPs still found at 18 months of age can be predicted.

Method: This prospective longitudinal study of 73 VP/VLBW and 105 FT infants utilized a standard interview of mothers to assess regulatory problems among the infants at term, 3, 6, and 18 months of age.

Results: Few differences were found between VP/VLBW and FT infants in the first 6 months. At 18 months, VP/VLBW infants had more single sleeping (RR=2.2, CI=1.3 to 3.7), feeding (RR= 1.4, CI= 1.03 to 1.8), and multiple RPs (RR=1.7, CI=1.02 to 2.8) than FT infants. In VP/VLBW infants, RPs as early as 3 months and in FT infants RPs as early as 6 months predicted RPs at 18 months. Those infants who had persistent RPs in the first 6 months of life were more likely to still have RPs at 18 months.

Conclusions: VP/VLBW children are at slightly increased risk for RPs at term and in the second year of life. Clinicians should be aware that RPs that persist across the first 6 months point to increased risk of continuing RPs into toddlerhood in both VP/VLBW and FT infants.

Keywords: preterm birth, regulatory problems, crying, feeding, sleeping, infancy.

INTRODUCTION

Approximately, 20% of full-term healthy infants experience regulatory problems (RPs) defined as excessive crying, sleeping, or feeding problems during the first year of life.^{1,2} These are transient in the majority of cases.³ Early RPs may be associated with trajectories of dysregulation into childhood⁴ and subsequent cognitive, behavior and attention problems,⁵⁻¹¹ especially if crying or feeding problems persist beyond the age of 3 to 4 months.^{1-3,6,12-14} In addition, multiple RPs, i.e. having two or three single RPs at the same time, increases the likelihood of later behavior problems.^{11,13}

There is some suggestion that preterm birth is associated with more RPs in early infancy.¹⁵⁻¹⁸ Others have not found an association between preterm birth and increased crying or sleeping problems.¹⁹⁻²¹ Feeding problems, on the other hand, have been consistently found to be more frequent after preterm birth.^{15,22-28} Previous studies of preterm populations were usually of small sample size or they just looked at single RPs.^{20,29-31} None, as far as we are aware, examined whether VP/VLBW and FT infants differ in early crying, sleeping and feeding or have multiple RPs more often beyond 6 months of age.

The aims of the current study were: 1) to examine if there is a difference in prevalence of single and multiple RPs among VP/VLBW and FT infants at term, 3 months, 6 months and 18 months of age; 2) to determine whether RPs at 18 months can be predicted by early RPs and whether prediction is enhanced if RPs persist across the first 6 months.

METHODS

Participants

Caretakers of 112 infants who were born VP/VLBW (<32 weeks of gestation or <1500 gr) in three neonatal units were approached during an 18 months period (See Appendix 1 for a detailed description). Seventy six caretakers of 90 VP/VLBW infants participated at the first assessment point at term. Recruitment of full-term children was conducted in the postnatal wards of the same hospitals within 48 hours of birth. One hundred and fifteen FT infants (37- 42 weeks gestation), matched for socio-economic status, sex and multiple birth and their caretakers (N=98) were also recruited from the same units (see ³² for a detailed description).

Participants were assessed at term, 3 months, 6 months and 18 months of age corrected for prematurity. Seventeen VP/VLBW and 10 FT infants did not complete the study until 18 months of age. VP/VLBW participants who did not complete the study (N= 17) differed from participants who remained in the study in that they had significantly higher medical risk neonatally ($F(1, 88) = 4.5, P < .05$) and had parents with lower income ($X^2(1,105) = 10.6, P = .005$) (Table 1). Otherwise, those who dropped out did not differ from those who remained in the study on birth weight, rates of SGA and gestational age or maternal education.

The final sample with complete longitudinal data comprised of 73 VP/VLBW (63 caretakers) and 105 FT infants (89 caretakers). VP/VLBW sample included 69 (94.5%) infants below 32 weeks of gestational age and 4 (5.5%) infants above or equal to 32 weeks of gestational age but with birth weight below 1500g. VP/VLBW and FT samples did not differ in terms of gender, multiple births, maternal age, income, and maternal education. VP/VLBW infants were significantly less likely to be breastfed at term ($X^2(1,178) = 9.81, P = .002$) than

FT infants. However, there were no differences in feeding type at 3 months ($X^2(1,177) = 3.31$, $P = .07$) and 6 months ($X^2(1,167) = .027$, $P = .87$) (See Table 1).

Measures

Background Measures. Medical risk was a composite of the following variables:

Neurosensory deficits, rehospitalisation, surgical procedures, and prolonged oxygen dependency assessed from medical notes and interviews at 3 months. Neurosensory deficits were defined as clinically significant deficits in hearing, vision, muscle tone or presence of hydrocephalus. Re-hospitalization was defined as whether the infant was readmitted to the hospital after discharge from the neonatal unit or not. Surgical procedures were defined as whether the infant had any surgery (e.g. for Patent Ductus Arteriosus, Necrotizing Enterocolitis) or not. Lastly, oxygen dependency was defined as oxygen use of more than 21% (1: never, 2: oxygen dependency still at term, 3: oxygen dependency still at 3 months). Additionally, Respiratory Distress Syndrome (RDS) and Bronchopulmonary Dysplasia (BPD) were recorded. RDS was recorded based on X-ray evidence at three levels: mild, moderate and severe.³³ BPD was defined as the need for supplemental oxygen use for more than 28 days^{33,34} in addition to chest X-rays of lung changes and coded as a dichotomous variable. Income was divided into 3 groups based on gross family income per annum: 1) 0-£25000, 2) £25000- £40000, 3) >£40000. Maternal education was divided into 3 groups based on years of education: 1) <10 years (not completed), 2) 10 years (basic), and 3) > 10 years (further education).

Regulatory Problems (RPs). A standard structured interview about crying, sleeping and feeding problems was conducted at term, 3, 6 and 18 months. Definition of crying, sleeping and feeding problems were derived from the literature (Table 2).

A crying problem was defined by the presence of at least one of three criteria (excessive duration of crying, difficult to soothe, mother's perception of crying as very distressing).^{5,7,14,20,35}

Sleeping problems were measured with 3 items at all measurement points. Participants were considered as having sleeping problems when at least one of the following criteria was present: a) woke up more than one time per night, b) took longer than 30 minutes to settle infant to sleep, c) the longest duration without waking up was less than 5 hours.

Feeding problems were measured with 2 summary items at term, 3, 6 and 18 months.

Problems in oral-motor functioning were measured with the following three items: a) stopping after a few sucks, b) excessive dribbling/difficulty swallowing, c) gagging/choking during the feed. Participants were dichotomized into two groups: no oral-motor functioning problems (0 or 1 problem present) and oral-motor functioning problems (2 or 3 problems present). Faddy eating/food refusal was measured with one item (fighting against the bottle/breast) at term, 3 and 6 months. At 18 months, a faddy eating/food refusal scale was created including the following variables: Eats too little, leaves most of the food offered, poor appetite, picky eater, slow eater, refuses to eat lumpy food, or even refuses to eat puree selectively. Internal consistency of this scale was high; .81 for the VP/VLBW and .74 for FT. Participants were categorized as having faddy eating/food refusal problems if they had 5 or more problems.

Participants were categorized as having multiple RPs if they had two or three single RPs.

Control Variables. Breastfeeding has previously been found to be related to more frequent sleeping problems and decreased feeding problems in infancy.^{15,21,36} In preterm infants, breastfeeding has been reported to increase the duration of crying.³⁷ Based on these findings, mothers were asked about how they fed their infant at term, 3 months and 6 months. They

were divided into two categories: breastfed and not breastfed. The breastfed category included infants who were only partially breastfed. Furthermore, CNS (Central Nervous System) problems have been suggested as influential factors in preterm infant's sleeping pattern.³⁸ In order to control for possible impact of CNS problems in preterm infants, brain ultrasound scans were used to measure haemorrhage, ventricular dilatation and parenchymal cysts at term (See Appendix 2 for a detailed description). The type of haemorrhage was coded as following: 0) none, 1) subependymal/choroidal one side, 2) intraventricular one side, 3) parenchymal one side, 4) subependymal/choroidal bilateral, 5) intraventricular bilateral, 6) parenchymal bilateral. Ventricular dilatation was coded as following: 0) no dilation, 1) less than 4mm one side, 2) more than 4mm one side, 3) less than 4mm bilateral, 4) more than 4mm bilateral. Parenchymal cysts were coded as: 0) none, 1) porencephalic cyst one side, 2) cystic leucomalacia one side, 3) porencephalic cyst bilateral, 4) cystic leucomalacia bilateral. All those infants whose early scans were scored ≥ 1 had repeat scans at a later date. According to the results of final scan (6th scan), infants were divided into two categories: CNS problem present (score ≥ 1) and not present (score = 0).

Statistical Analyses

Data were analysed with SPSS (IBM, version 21.0). One way ANOVA and chi-square test (X^2) were used to compare the dropouts and non-dropouts. Chi-square test was also used to compare the RPs of VP/VLBW and full-term groups at each time point. Contingency coefficients were computed as indices of the associations of RPs across measurement points. Binominal logistic regression was used to estimate the odds ratio of having RPs at 18 months. All analyses except for differences in frequencies at 18 months were adjusted for breastfeeding. Furthermore, analyses for VP/VLBW infants were adjusted for CNS problems. Statistical significance was defined as $P < .05$.

In the data analysis regulatory problems were considered as transient if they were present only at one measurement point (term, 3 months, or 6 months) in the first 6 months. If regulatory problems were present at two or three measurement points during the first 6 months, they were considered as persistent regulatory problems. VP/VLBW infants were assessed at term, 3, 6 and 18 months corrected for prematurity and controls at chronological age.

RESULTS

Differences between very preterm and full-term infants at term, 3 months, 6 months, and 18 months

Frequencies of single and multiple RPs are shown in Table 3.

There were little differences in RPs between VP/VLBW and FT infants. At term, VP/VLBW had slightly higher risk ratios of having crying, feeding or multiple regulatory problems than FT. At 3 months and 6 months, there were no significant differences between groups. At 18 months, VP/VLBW had more often single sleeping, feeding, and multiple RPs (See Table 3).

The impact of having lung disease (RDS, BPD) on RPs was further investigated in VP/VBW infants. Chi-square analysis revealed no significant differences between those who suffered from lung disease and who did not in RPs at all measurement points. Additionally, the impact of being SGA (Small for Gestational Age) was investigated. Results revealed no differences at any measurement point between those who were SGA and those who were AGA (Appropriate for Gestational Age). Furthermore, VP/VLBW infants who were SGA did not differ from full-term infants.

How Early Can We Predict Crying, Sleeping, and Feeding Problems at 18 Months?

Figure 1 illustrates the contingency coefficients between the 3 early measurement points and 18 months outcome for crying, sleeping and feeding RP in VP/VLBW and FT.

For FT infants, the contingency coefficient between early RPs and 18 months sleeping, feeding, and multiple RPs increased with age (i.e. 6 months had the highest correlation). This pattern was not evident for VP/VLBW infants for crying, sleeping and multiple RPs, where the highest correlation with 18 months was already found at 3 months. Only for feeding RPs, VP/VLBW infants followed the same association pattern as FT infants.

Associations between Persistence of RPs until 6 Months and RPs at 18 Months

In VP/VLBW infants, having either transient (i.e. at one measurement point) (OR= 3.3, CI= 1.2 to 5.8) or persistent RP (OR=4.2, CI= 1.4 to 12.9) in the first 6 months was associated with sleeping RP at 18 months. Furthermore, having persistent RPs at 3 measurement points (OR= 3.9, CI= 1.3 to 6.1) was significantly related to multiple RPs at 18 months in VP/VLBW infants.

In FT infants, having persistent RPs during the first 6 months of life (OR= 3.4, CI= 1.2 to 3.9) was also associated with sleeping RP at 18 months (Supplemental Table 1). Moreover, having persistent RP (OR= 3.5, CI= 1.2 to 5.9) was associated with multiple RPs at 18 months.

DISCUSSION

This study investigated early regulatory problems (crying, sleeping, and feeding) in VP/VLBW infants in comparison to FT infants during the first 18 months. Our findings indicate few differences between VP/VLBW and FT infants in the first 6 months of life but emerging differences in sleeping, feeding or multiple RPs at 18 months. For predicting 18

months RPs, associations were emerging slightly earlier (i.e. at 3 months) in VP/VLBW infants for crying, sleeping and multiple RPs than full term children. Moreover, persistence of any RP across the first 6 months increased the odds of having multiple RPs or sleeping RPs in both VP/VLBW and FT infants.

The prevalence of single and multiple RPs was similar to previous reports during the first 18 months of life.^{4,39,10,35,40} However, crying RPs in FT infants at 3 months (17.1%) was found to be lower than in one previous study (29%).⁴¹ Furthermore, in VP/VLBW infants, the prevalence of sleeping RPs at 18 months was 34% which was somewhat higher than the rates reported in previous studies (approximately 15%).^{21,42}

There were few differences between VP/VLBW and FT infants in sleeping, feeding or multiple RPs in the first 6 months but they emerged at 18 months. This is consistent with previous findings of no differences in crying patterns and durations between preterm and full-term infants before 3 months.^{19,20,43} Some differences were found in feeding skills, between VP/VLBW and FT infants both early at term when sucking coordination is important^{27,30,44} and after 6 months of age when processing of solids is required.^{24,45,46} Consistent with previous research, no differences in sleeping patterns between very preterm and full-term infants during the first 6 months of life was found.^{29,47,48} However, our finding that very preterm infants had increased odds of sleeping problems at 18 months contradicts findings of other studies.^{21,35,49} Higher sleeping problems in VL/VLBW infants might reflect insecure or disorganised attachment which has been shown to increase sleeping problems in full-term infants⁵⁰ and has been found to be more frequent in VP/VLBW toddlers.³²

Having any RP that persisted from term to 6 months increased the odds of having sleeping RPs or multiple RPs in both VP/VLBW and FT infants. Persistence of RPs has been repeatedly found to predict later behavior problems.^{3-5,12,51} Our findings support the

significance of persistence of RPs for predicting sleeping and multiple RPs in both VP/VLBW and FT infants in the toddler years. However, there were also some differences between full term and VP/VLBW infants in predicting 18 months RPs. In FT infants, regulatory problems at 18 months were mainly related to persistent regulatory problems at two or three measurement points in the first 6 months. Previous research showed that single or transient regulatory problems are less likely to lead to later adverse behaviour indicating early behavior adaptation in the first 6 months of life.^{14,52,53} In contrast, persistent or multiple problems experienced in the first 6 months have been consistently reported to increase the risk of later RPs or adverse outcomes in infants.^{2,3,5,13,54} This study suggests that VP/VLBW infants may be more susceptible to develop long term multiple problems and this is predicted at an earlier age. Single or multiple regulatory problems at term and 3 months already predicted 18 months sleeping and multiple regulatory problems in VP/VLBW but less so in FT infants. Similar findings have been recently reported in a longitudinal study of crying problems of preterm infants in Finland.¹⁸

In contrast, single crying or feeding RPs at 18 months were not predicted by early persistent RPs in both groups. Thus crying and feeding RPs were poorly predicted by early child behavior. Mother-infant interaction problems, maternal stress and maternal anxiety have been suggested as critical factors in developing crying and feeding problems.⁵⁵⁻⁶¹ Future research may take into account the impact of maternal mental health and/or mother-infant interaction in alleviating or leading to crying and feeding problems.

Strengths and Limitations

The strength of this study is the detailed definition of crying, sleeping and feeding problems. Most previous studies either used one or two indicators of the problems. Furthermore, to our

knowledge this is the first study to measure all three regulatory problems (crying, sleeping and feeding) in both very preterm and full-term infants during the first 18 months of life. Moreover, this study controlled for the impact of breastfeeding and CNS problems on regulatory problems. In addition, this study had a matched sample on the number of twins to control for parenting effects in VP/VLBW infants and controls equally.

There are also limitations. Regulatory problems were assessed with a standard interview using mothers as data source. Using diaries or observational methods would have provided more objective information than parental interviews; however, they are prone to lower and selective participation rates.⁶² Furthermore, our sample included 4 infants with equal or above 32 weeks of gestational age but with a very low birth weight. We included these infants in our study for two reasons: a) exclusion did not change our findings and b) other studies report on very preterm and very low birth weight (VP/VLBW) sample combined.⁶³⁻⁶⁵

Conclusions

VP/VLBW infants are only at slightly increased risk for experiencing more regulatory problems at term and in the second year of life than healthy full term children. In particular, persistent regulatory problems in the first 6 months forebode increased sleeping and multiple RPs at 18 months in both VP/VLBW and full term children. Clinicians should be aware that persistency of crying, sleeping or feeding problems in the first 6 months and their co-occurrence increase the risk of long-lasting problems which might still have an impact on parents a year later.

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Figure Legends

Figure 1. Associations between RPs at early months (term, 3 months, 6 months) and 18 months

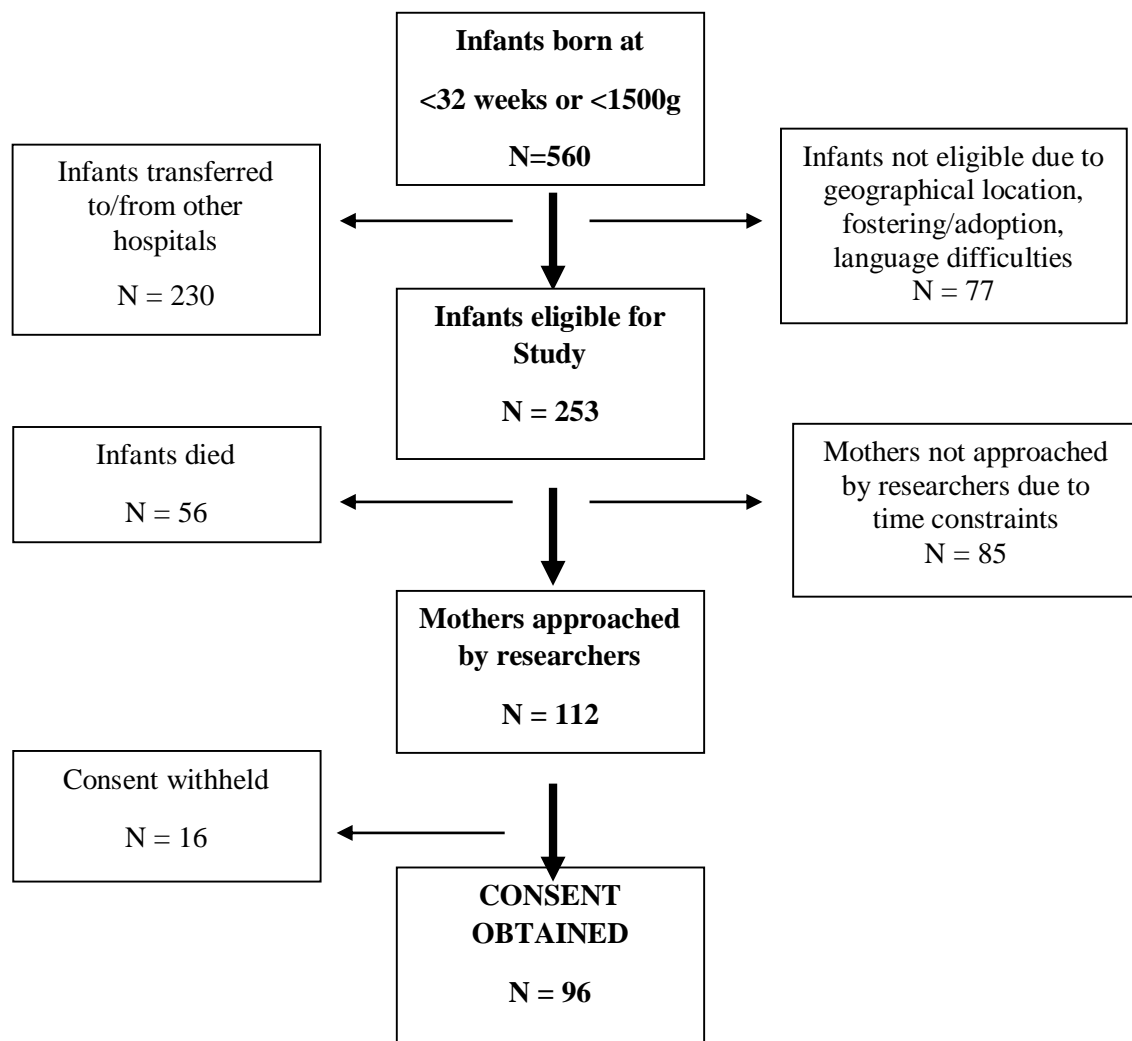
Appendix 1

Full Description of the Recruitment Procedure for VP/VLBW Infants

The principal selection criterion for entry into the study was that the infants had to have been born at or before 32 completed weeks of gestation, or weighing less than 1500g, at one of the three participating hospitals in the South East of England. There were, however, certain exclusion criteria:

- If the infant was transferred into or out of the participating Unit after birth and prior to discharge home (medical notes remain at hospital of origin, and would therefore not be available);
- If the parental home was more than 2 hours drive from the hospital (impracticality of follow-up assessments);
- If the infant's mother only had limited English (interviews would have been difficult);
- If the infant was being sent for fostering/adoption.

Figure: Recruitment Procedure for VP/VLBW Infants



As the flow chart above shows, after excluding infants on the basis of the stated exclusion criteria there were 253 potential participants for the study. Unfortunately, 56 of these infants died within the first few weeks after birth. In addition, due to time constraints, a maximum of just six infants per month could be recruited (based on due date of delivery). Thus there were 112 infants eligible to be recruited into the study.

The two researchers each recruited and followed up approximately half of the final sample up to, and including, the 3-month assessment. A team of researchers followed up the infants at 18 months. Designation of a particular researcher to each hospital simplified recruitment procedures and also facilitated good relationships with the hospital staff.

Recruitment Procedure

Once a target infant's condition had stabilised and he/she no longer required mechanical ventilation, the researcher introduced herself to the mother and explained the aims of the Study and what participation would involve should she agree to the inclusion of her infant. An information sheet was also given to her at this time. A few days later, the mother was approached and asked whether she had had a chance to read the information sheet, had any questions about it, and was prepared to participate. If she agreed, written consent was obtained in the presence of an independent witness, and the infant was thus recruited into the study. Copies of the study information sheet and consent form are available from the authors

Consent Rate

The final consent rate was 86% (96 out of 112). Sixteen mothers declined to take part in the study: two cited cultural/religious objections to the research; six cited lack of willingness to put themselves or their infants through any more stress; four felt that they could not afford the time due to demands of older children and/or work commitments; and three did not wish to be involved in research due to dissatisfaction with the hospital care. One mother refused to participate because her infant was suspected of having serious brain damage.

The infants who were eligible to participate in the study but for whom maternal consent was not obtained did not differ from the study sample as regards gestational age or birth weight (Please see table below).

Table: Comparison of Final Sample with Non-Consents

	N	Gestation (weeks)	t	Birth weight (g)	t
Non-Consents	16	29.6	.43	1287	.27
Sample	96	29.7		1282	

Of the 96 infants actually recruited into the study, five were lost prior to the term assessment (in four cases they were not possible to contact and/or repeatedly failed to attend appointments, in the fifth case the mother developed a psychiatric illness and the infant was temporarily fostered before the father became the primary care-giver). Furthermore, one infant unfortunately died before the 3-month assessment. Thus, the final sample of the study at term assessment comprised 90 infants.

Appendix 2

Ultrasound Scans of Brain

For the VP/VLBW infants one or more ultrasound scans of the brain were performed during initial hospitalisation. Table 1 describes the coding system used to score the scans.

Table 1: Scoring of Ultrasound Scans of the Neonatal Brain

Score	Haemorrhage	Ventricular Size	Parenchymal Cysts
0	None	No Dilatation	None
1	Subependymal/choroidal 1 side	< 4mm 1 side	Porencephalic cyst 1 side
2	Intraventricular 1 side	> 4mm 1 side	Cystic leucomalacia 1 side
3	Parenchymal 1 side	< 4mm bilateral	Porencephalic cyst bilateral
4	Subependymal/choroidal bilateral	> 4mm bilateral	Cystic leucomalacia bilateral
5	Intraventricular bilateral		
6	Parenchymal bilateral		

Table 2 shows the frequency data for the variables described above. All those infants whose early scans were scored ≥ 1 had repeated scans at a later date.

Table 2: Frequency Data on Neonatal Ultrasound Scans of Brain

		Scan 1	Scan2 (N=40)	Scan3 (N=25)	Scan4 (N=17)	Scan5 (N=11)	Scan6 (N=6)
Haemorrhage	Subependymal/choroidal 1 side	1	2	1	1	0	0
	Intraventricular 1 side	2	3	2	2	1	0
	Parenchymal 1 side	0	0	0	0	0	0
	Subependymal/choroidal bilateral	0	0	0	0	0	0
	Intraventricular bilateral	0	1	1	1	1	0
	Parenchymal bilateral	0	0	0	0	0	0
Ventricular Size	< 4mm 1 side	5	5	3	1	1	1
	> 4mm 1 side	0	0	0	0	0	0
	< 4mm bilateral	0	1	1	0	0	0
	> 4mm bilateral	0	0	0	1	1	1
Parenchymal Cysts	Porencephalic cyst 1 side	0	2	2	1	2	3
	Cystic leucomalacia 1 side	0	0	0	0	0	0
	Porencephalic cyst bilateral	0	0	0	0	0	0
	Cystic leucomalacia bilateral	0	0	0	0	0	0

According to the results of final scans (scan 6), there were 5 infants who showed evidence of neurological damage.