

# Trends in incidence of cranial ultrasound lesions and cerebral palsy in very low birthweight infants 1982-93

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## Abstract

**Aim**—To evaluate the effects of changing perinatal practice on outcome in terms of cranial ultrasound appearances and subsequent cerebral palsy rates in survivors.

**Methods**—A tertiary neonatal centre based prospective cohort study was undertaken of very low birthweight infants, in three 4 year periods: 1982-5, 1986-9, 1990-3. Rates of survival, parenchymal cerebral haemorrhage (PH), and leucomalacia on cerebral ultrasound scans, and cerebral palsy (CP) at the age of 3 years were compared. Antenatal steroid prophylaxis and postnatal surfactant use were also compared.

**Results**—VLBW infants (1722) were admitted over the 12 years, of whom 1268 (73.6%) were discharged home. Neonatal survival increased significantly over the three periods (69.2%, 72.9%, 79.7%;  $p < 0.0001$ ). PH declined from 14.9% to 10.5% ( $p = 0.032$ ) after 1990 as did CP rate (10.9% to 7.3%;  $p = 0.046$ ). The use of antenatal steroids and postnatal surfactant greatly increased during this period. Steroid use was significantly associated with increased survival (OR 3.34, 2.31-4.79), decreased PH (OR 0.44, 0.28-0.71), and decreased risk of CP in survivors (OR 0.47, 0.27-0.81) after standardising for gestation, birthweight, sex, place and mode of delivery. Similar effects for surfactant did not remain significant after steroid use had been accounted for.

**Conclusion**—Improved survival in VLBW infants since 1990 has been accompanied by a fall in PH and subsequent CP rates in survivors. This change is most likely to be due to the greater use of antenatal steroid prophylaxis.

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Keywords: very low birthweight; cerebral haemorrhage; cranial ultrasound; cerebral palsy; antenatal corticosteroid

Cerebral palsy in childhood is a defect in movement and/or tone following a lesion to the developing brain.<sup>1</sup> In those born at term the timing and cause of the lesion is usually believed to be antenatal.<sup>2</sup> This may not be the same for very preterm infants, in whom cerebral lesions on postnatal cranial ultrasound scans are associated with subsequent cerebral palsy in many cases. This is particularly true of parenchymal haemorrhage (PH) and infarction.<sup>3</sup> Several major perinatal centres have reported that cerebral haemorrhage, diag-

nosed in the neonatal period using cranial ultrasound imaging, has become less frequent in recent years. It has been suggested, however, that haemorrhagic lesions may be being replaced by ischaemic ones such as periventricular cystic leucomalacia (PVL).<sup>4,5</sup> If this is so, the neurodevelopmental outcome of very preterm survivors is unlikely to be improving with the apparent decline in the incidence of cerebral haemorrhage.

The aim of this study was to determine if the decline in the incidence of cerebral haemorrhage in recent years previously observed in a referral unit population of very low birthweight (VLBW) infants, has been associated with a change in the prevalence of cerebral palsy (CP) in the survivors 3 years later, and to examine changing perinatal practices that may have been responsible.

## Methods

Since 1980, a computerised database containing information on all VLBW infants admitted to Mersey Regional Neonatal Intensive and Special Care Unit has been prospectively maintained. Data describing clinical and demographic variables, as well as cranial ultrasound scan appearances and a summary of neurodevelopmental outcome are available. Antenatal steroids and postnatal surfactant were taken as having been used if one or more doses were recorded as having been given.

Cranial ultrasound records have been reported by a single observer (the author) and represent a summary of multiple examinations during the infant's stay on the unit. For the purposes of this study, only the presence of parenchymal haemorrhage and infarction have been recorded as PH. Periventricular cystic leucomalacia (PVL), often followed PH, but was only recorded here separately when it was observed without preceding PH. The presence of PH and or PVL is referred to as an intraparenchymal lesion (IPL).

Neurodevelopmental follow up was carried out by one of four neonatal consultant paediatricians from the unit on a regular basis until the infants were 5 years old. Over 80% of the infants were followed up in this way, but information on most of the remainder was obtained from letters and questionnaires sent to other consultant paediatricians, general practitioners, health visitors, and occasionally the child's parents. Ascertainment of CP cases was also checked against the Regional Cerebral Palsy Register.<sup>6</sup> The neurodevelopmental outcome variable used for this study was cerebral palsy diagnosed at the examination made nearest to

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Table 1 Demographic and clinical data on three 4 year cohorts

	1982-5	1986-9	1990-3
Admitted	622	579	521
Died on unit	191	157	106
Discharged	431 (69.2%)	422 (72.9%)	415 (79.7%) <i>p</i> <0.001
Died later	15	18	7
Antenatal steroids	117	23	251
Surfactant	0	3	220
PH	93 (14.9%)	82 (14.2%)	55 (10.5%) <i>p</i> =0.032
PVL	8	19	9
IPL	101 (16.2%)	101 (17.4%)	64 (12.2%) <i>p</i> =0.048
No scan	2	4	16
Lost to follow up	5	17	10

3 years of age. Those cases in which spasticity predominated were classified by the limbs mainly affected as diplegia, hemiplegia, and quadriplegia. The few remaining cases were termed "other."

Data were analysed and presented for three 4 year periods: 1982–5, 1986–9, and 1990–3. The significance of differences seen was tested using the  $\chi^2$  test, or  $\chi^2$  test for trend, as appropriate. The influence of antenatal corticosteroid prophylaxis and postnatal surfactant treatment on outcomes was assessed using logistic regression to standardise for gestation, birthweight, male sex, place and mode of delivery. Results are presented as odds ratios together with 95% confidence limits.

### Results

During the 12 years covered by this study, 1722 VLBW infants were admitted to the unit and 1268 (73.6%) were discharged home. The proportion of survivors increased significantly over the three time periods (table 1) (*p*<0.0001). Forty infants died before the age of 3 years; 32 were lost to follow up. A significant decline in PH from 14.9% to 10.5% ( $\chi^2$  for trend 4.46, *p*=0.032) and for IPL, 17.4% before and 12.2% after 1990 (*p*=0.048) was observed. The decline in PH was not accompanied by a rise in isolated PVL. Mortality for infants with PH was 62% and remained similar throughout the study. Twenty two infants did not have an ultrasound scan because they died too soon after birth.

From neurodevelopmental follow up and other enquiries, 116 cases of cerebral palsy had been ascertained by the age of 3 years (table 2). Of the infants lost to follow up, none had had PH or PVL. CP prevalence remained at 10.9% between 1982 and 1989, but declined significantly to 7.3% between 1990 and 1993 (*p*=0.046). When the types of CP were examined for the three periods (table 3), spastic diplegia occurred in similar numbers, but a decline in spastic hemiplegia and quadriplegia appeared to account for the fall in overall prevalence of CP since 1990. Overall, 65

Table 2 Clinical and outcome data on three 4 year cohorts

	1982-5	1986-9	1990-3
Data at 3 years	411	387	398
PH	35	30	22
PVL	5	14	7
IPL	40	44	29
CP	45 (10.9%)	42 (10.9%)	29 (7.3%) <i>p</i> =0.046
Antenatal steroids	97	18	208
Surfactant	0	2	154

Table 3 Types of cerebral palsy seen in three 4 year cohorts

	1982-5	1986-9	1990-3
All cerebral palsy	45	42	29
Diplegia	14	12	12
Hemiplegia	23	12	9
Quadriplegia	7	17	4
Others	1	1	4

infants with CP at 3 years had an IPL on ultrasound scan in the neonatal period, giving a positive predictive value for IPL of 58% and a negative predictive value of 95%.

The use of any antenatal corticosteroid prophylaxis (one or more doses) was highest after 1990, as was the use of exogenous pulmonary surfactant postnatally. Steroid use was associated with increased survival (OR 3.34, 2.31–4.79), decreased PH (OR 0.44, 0.28–0.71) and a decreased risk of CP in 3 year survivors (0.47, 0.27–0.81), after standardising for gestation, birthweight, male sex and place and mode of delivery. These results also remained significant after allowing for surfactant use in the analysis. A similar trend was seen for surfactant use for increased survival (OR 2.21, 1.50–3.26), decrease PH (OR 0.65, 0.41–1.05) and CP (OR 0.56, 0.29–1.11), but these effects were lost when steroid use was introduced into the analysis.

### Discussion

The improving survival of VLBW infants has been observed for at least three decades, but the effect that this has had on CP rates has been far from clear. CP rates of 10–15% have been generally reported in cohorts whether defined by hospital centre or area of residence,<sup>7</sup> and CP in VLBW infants now accounts for about 25% of all CP cases. Hagberg *et al* reported an overall decline in CP in Sweden from 1959–70 and an increase from 1971–8 in the face of a continued decline in perinatal mortality.<sup>8</sup> The changes were mostly associated with changes in the incidence of diplegias in preterm infants. Pharoah *et al* described data from a regional cerebral palsy register and noted a marked increase in the prevalence of CP in VLBW infants during the 1970s in the Mersey Region, which he attributed to improved survival of prenatally impaired infants, although he acknowledged that other explanations were possible.<sup>9</sup>

Robertson *et al* compared two cohorts of preterm infants of 500–1250 g from a regional programme in 1978–9 and 1988–9, and concluded that while survival had doubled, CP rates for this group remained unchanged.<sup>10</sup> In a similar hospital based study Tudehope *et al* produced much the same findings.<sup>11</sup> A 20 year population based study in Norway showed a fall in CP rates, overall, and also for VLBW infants despite a 50% reduction in perinatal mortality in all weight groups.<sup>12</sup> The authors accounted for this by the reduction in the incidence of low birthweight in the population over the study period, a trend not observed elsewhere.

O'Shea *et al* described a regional cohort of VLBW infants born between 1982 and 1984 and showed a marked decline in neonatal

mortality after 1990, which was accompanied by a similar fall in CP rate.<sup>13</sup> Adjustment for surfactant use accounted for the decline in mortality, but not CP rate. O'Shea *et al* do not refer to steroid use or to ultrasound diagnosis of cerebral lesions. This study has also shown an improvement in survival over the 12 year period, as well as a falling CP rate since 1990. Surfactant use is also associated with improved survival but not significantly with subsequent risk of CP. However, the apparent protective effect of increased antenatal steroid prophylaxis is much greater than that of surfactant, and remains significant after allowing for surfactant use.

This study has its limitations. The diagnosis of PH and PVL has been achieved using a variety of ultrasound scanners over the 12 year period, and using higher transducer frequencies in the more recent periods. This will tend to increase the diagnosis of lesser lesions. By using major lesions only and a single reporter, inconsistencies over time should have been minimised. The mortality in infants with PH remained high at over 60% throughout the study, although there was no policy for withdrawing intensive care based on ultrasound findings alone. About 30 infants in the period 1986-9 were subjects in two blinded multicentre controlled trials of surfactant treatment, and whether they received surfactant or were controls is not recorded in the case notes. They have been marked as not having had surfactant on the database. This would have tended to reduce any effect that surfactant use might have had on the incidence of CP. It was not possible to distinguish between complete or partial courses of antenatal steroids. It has been suggested, however, that while a full course is needed to obtain maximum protection against respiratory distress, even a single dose shortly before delivery is cerebroprotective.

The follow up was performed by many different observers, although most of it was done by four experienced neonatal paediatricians. Most, but not all, of the clinicians were blind to the early ultrasound findings. By using a major outcome variable such as CP, it was hoped to overcome these problems, although it is possible that differences in interpretation of the clinical neurological signs occurred. At the age of 3 years most of the children diagnosed as having CP had also been seen at a Child Development Centre and had been more extensively evaluated. The use of data collected from other observers, while less reliable, was felt to be justified in an attempt to make the follow up as complete as possible. Use of the Regional Cerebral Palsy Register acted as a further check. Some of the children lost to follow up may have had CP, although the absence of PH or PVL in this group makes this less likely. Ascertainment of CP cases increases with time, and this is especially a problem when historical comparisons are being made, as more

recent periods will tend to contain fewer cases. The use of the assessment nearest to 3 years should have avoided this effect.

Spastic diplegia has been the form of CP most strongly associated with preterm birth, a point noted by Freud during the 19th century.<sup>14</sup> The high rates of CP seen more recently in VLBW survivors of intensive care have included a much higher proportion of spastic hemiplegia and quadriplegia, with attendant poor outcomes.<sup>7</sup> Other forms of CP are much less prevalent in VLBW infants. In this study the numbers of children surviving with spastic diplegia were similar in all three periods, and the apparent reduction in CP rate after 1990 is accounted for by a fall in spastic hemiplegias and quadriplegias. It has previously been shown that, unlike diplegias, hemiplegias and quadriplegias are mostly related to variables associated with intrapartum and postpartum events.<sup>15</sup> Antenatal steroids may be acting as a cerebral protectant in these vulnerable infants.

The effect of the introduction and development of neonatal intensive care has been mainly to increase intact survival, while the overall numbers of VLBW infants with CP has usually increased rather less. It is likely that antenatal steroid prophylaxis is the first example of a perinatal treatment, apart from perhaps exchange transfusion, which has actually reduced the risk of CP in VLBW infants.

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