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Perinatal factors and adverse outcome in extremely low birthweight infants

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SUMMARY Perinatal factors associated with death or disability at 2 years were identified in an inborn cohort of 196 live births with a birth weight of 500–999 g. Antepartum haemorrhage, multiple pregnancy, breech presentation, perinatal asphyxia, hypothermia on admission, hyaline membrane disease, persistent pulmonary hypertension, severe respiratory failure, and intraventricular haemorrhage were associated with increased mortality. Factors associated with increased survival included maternal hypertension, caesarean birth, increasing maturity or size at birth, female sex, and fetal growth retardation. Stepwise multiple discriminant function analysis showed that six factors correctly classified the outcome in 83% of infants: intraventricular haemorrhage was the most important factor followed by the presence of acidosis and hypoxia in the early neonatal period, birth weight, pre-eclamptic toxaemia, and caesarean birth. This study also showed that intraventricular haemorrhage, seizures, antepartum haemorrhage and delay in regaining birth weight were associated with increased disability among survivors.

Recent advances in perinatal intensive care have resulted in improvements in survival rate of extremely low birthweight (<1000 g) infants[1] and disability rate in extremely low birthweight survivors.[2] It is important to identify perinatal factors that increase the risk of death or disability in this population as further improvement in outcome depends on strategies that obviate such unfavourable perinatal influences. The aims of the present study are to document the two year survival and disability rates in a cohort of extremely low birthweight infants born in a single tertiary care perinatal centre and to define perinatal factors associated with death or disability.

Patients and methods

The study population consisted of live births born between 1 January 1977 and 31 December 1982 at Queen Victoria Medical Centre with a birth weight of 500–999 g. Live birth was defined as an infant who had a heartbeat, respiratory activity, or voluntary muscle movement. During this six year period there were 78 stillbirths, 196 live births, and 101 neonatal deaths in this birthweight category. The stillbirth rate was 285 per 1000, neonatal mortality 515 per 1000, and perinatal mortality 653 per 1000.

All survivors were assessed at 2 years of age, corrected for prematurity. They were given a clinical, neurological, and psychological assessment, and the Bayley scales of infant development were administered. Disability was defined as cerebral palsy of any type or severity, blindness, sensorineural deafness, and developmental delay (mental developmental index more than 2SD below the mean on the Bayley scales).

Obstetrical, delivery, and neonatal data were prospectively coded during the study period, checked, and transferred to magnetic tape for analysis with the use of the Statistical Package for Social Sciences. Statistical analysis was carried out by Student's t test for quantitative variables and χ^2 analysis with Yates's correction for categorical variables. Stepwise discriminant function analysis was then carried out on the independently significant factors identified.

Results

Two year outcome. The survival rate of the 196 live births and after correction for 10 (5%) major congenital malformations is shown in Table 1. Six infants had oesophageal atresia and tracheo-oesophageal atresia (of whom one also had trisomy 21 and one had vertebral defects, imperforate anus, tracheo-oesophageal fistula, and radial and renal

Table 1 *Two year survival and disability data*

Birth weight (g)	*No of infants*	*No with malformation*	*Survival (uncorrected) No (%)*	*Survival (corrected) No (%)*	*No (%) of survivors with disability*
500–599	28	0	3 (11)	3 (11)	1 (33)
600–699	29	0	7 (24)	7 (24)	2 (29)
700–799	36	5	15 (42)	15 (48)	4 (27)
800–899	55	3	33 (60)	33 (63)	8 (24)
900–999	48	2	30 (63)	30 (65)	9 (30)
Total	196	10	88 (45)	88 (47)	24 (27)

dysplasia, and one each had neural tube defect, congenital hydrocephalus, trisomy 21, and multiple anomalies. Of the 108 deaths, 37 (34%) occurred in the delivery room before admission to the neonatal intensive care unit, 33 (31%) on day 1 after admission, 16 (15%) on days 2–7, 15 (14%) on days 8–27, and seven (6%) beyond the postneonatal period up to 2 years of age. Of the 88 survivors, cerebral palsy occurred in 14 (16%) children, blindness in two (2%), sensorineural deafness in two (2%), and developmental delay in 12 (14%). As six children had two disabilities each a total of 24 (27%) had disability.

Obstetrical and delivery factors and survival. Fifty seven obstetrical and delivery factors were analysed in 88 survivors and 98 deaths (10 malformations excluded). Table 2 lists the factors that were significantly different in the two groups. Stepwise discriminant function analysis for obstetrical and delivery data showed that nine factors correctly classified the outcome in 80% of infants (Table 3). The size of the standardised canonical discriminant function coefficient indicated that the mode of delivery and the condition at birth were the most important factors.

Table 2 *Significant obstetrical and delivery factors in survivors* v *deaths. Data expressed as number (percentage) or mean (SD)*

Factors	*Survivors (n=88)*	*Deaths (n=98)*	*p Value*
	No (%)	*No (%)*	
Pre-eclamptic toxaemia	18 (20)	5 (5)	0·0032
Essential hypertension	9 (10)	2 (2)	0·0402
Bleeding:			
In first trimester	9 (10)	24 (2)	0·0188
In second trimester	27 (31)	47 (48)	0·0242
Multiple pregnancy	6 (7)	20 (20)	0.0140
Private health insurance	63 (72)	55 (56)	0·0419
Use of fetal cardiotocography	30 (34)	13 (13)	0·0014
Measurement of maternal oestriols	17 (19)	4 (4)	0·0046
Breech or non-vertex presentations	30 (34)	52 (53)	0·0141
Caesarean section	30 (34)	18 (18)	0·0227
Female sex	57 (65)	47 (48)	0·0309
Small for gestational age	15 (17)	4 (4)	0·0097
	Mean (SD)	*Mean (SD)*	
Apgar score:			
At one minute	4·6 (2·3)	2·8 (2·2)	0·0001
At five minutes	6·6 (1·9)	4·1 (2·9)	0·0001
Gestational age (wk)	27 (2)	25 (2)	0·0001
Birth weight (g)	842 (107)	719 (143)	0·0001
Birth length (cm)	35 (2)	32 (3)	0·0001
Birth head circumference (cm)	24 (1)	22 (2)	0·0001
Birth centile:			
Weight	43 (26)	54 (17)	0·0010
Length	35 (25)	51 (21)	0·0001
Head circumference	34 (18)	41 (18)	0·0190

Neonatal factors and survival. Forty nine neonatal factors were included in a further analysis of 88 survivors and 69 deaths. Excluded from the group of infants who died were 10 with malformation and 29 normally formed infants who did not have neonatal data as they died in the delivery room. Table 4 lists the neonatal factors that were significantly different in the two groups. The clinical diagnosis for hyaline membrane disease[3] and persistent pulmonary hypertension[4] was based on definitions previously described. Until late 1980 the diagnosis of intraventricular haemorrhage was made on clinical grounds; since that time, routine real time cerebral ultrasound scans have been performed in all extremely low birthweight infants. Stepwise discriminant function analysis of all perinatal data, including neonatal factors, showed that six factors correctly classified the outcome in 83% of infants (Table 5). Intraventricular haemorrhage was the most impor-

Table 3 *Stepwise discriminant function analysis of obstetrical and delivery factors associated with increasing survival*

Factors	*Discriminant function coefficient*
Caesarean section	0·42419
Apgar score at five minutes	0·42384
Higher gestational age	0·40075
Higher birth weight	0·39062
Lower birth length centile	0·32300
Pre-eclamptic toxaemia	0·31013
Singleton pregnancy	0·23447
No bleeding in first trimester	0·20732
Female sex	0·19549

tant factor, followed by the presence of acidosis and hypoxia in the early neonatal period.

Perinatal factors and disability. One hundred and thirty eight perinatal factors were analysed in 64 normal survivors and 24 survivors with disability. Four factors were significantly different in the two groups (Table 6). The two perinatal risk factors that related to both death and disability were antepartum and intraventricular haemorrhages. Stepwise discriminant function analysis was not appropriate because of the paucity of significant variables and the fairly small number of children with disability.

Table 4 *Significant neonatal factors in survivors* v *deaths. Data expressed as No (%) or mean (SD)*

Factors	*Survivors (n=88)*	*Deaths (n=69)*	*p Value*
	Mean (SD)	*Mean (SD)*	
Body temperature on admission (°C)	35·4 (8·8)	34·8 (13·4)	0·0050
Base deficit on admission (mmol/l)	6·7 (0·5)	10·7 (0·9)	0·0020
Oxygen requirement on admission (%)	56 (25)	68 (27)	0·0070
Lowest pH on day 1	7·20 (0·12)	7·06 (0·23)	0·0001
Lowest pH on day 2	7·25 (0·11)	7·15 (0·19)	0·0020
Lowest arterial partial pressure of oxygen on day 1 (mmHg)	55 (22)	34 (21)	0·0001
Lowest arterial partial pressure of oxygen on day 2 (mmHg)	52 (12)	39 (22)	0·0010
	No (%)	*No (%)*	
Hyaline membrane disease	23 (26)	32 (46)	0·0330
Paralysis with tubocurarine	8 (9)	26 (38)	0·0001
Persistent pulmonary hypertension	10 (11)	23 (33)	0·0010
Tolazoline treatment	3 (3)	10 (14)	0·0271
Intraventricular haemorrhage	24 (27)	42 (61)	0·0001

Table 5 *Stepwise discriminant function analysis of all perinatal factors associated with increasing survival*

Factors	*Discriminant function coefficient*
No intraventricular haemorrhage	0·68567
Higher pH on day 2	0·51650
Higher arterial partial pressure of oxygen on day 2	0·42021
Higher birth weight	0·32777
Pre-eclamptic toxaemia	0·25692
Caesarean section	0·19158

Table 6 *Significant perinatal factors in normal survivors* v *those with disability. Data expressed as No (%) unless otherwise stated*

Factors	*Normal survivors (n=64)*	*Survivors with disability (n=24)*	*p Value*
Antepartum haemorrhage	22 (34)	14 (60)	<0·05
Intraventricular haemorrhage	12 (19)	12 (50)	<0·01
Neonatal seizures	6 (9)	8 (33)	<0·01
Mean (SD) age when birth weight regained (days)	18 (7)	23 (10)	<0·02

Discussion

Although selected independent perinatal factors that affected survival of extremely low birthweight infants or those born at 24–28 weeks' gestation have previously been reported,[5–7] only three studies have an exclusively inborn population, having excluded outborn infants selectively referred for admission to a tertiary neonatal intensive care unit. There is a profound selection bias in the process of referral for treatment for outborn infants,[8] and we have previously shown that perinatal factors associated with survival in a population of infants who weighed 1500 g or less were substantially different between the inborn and outborn subgroups.[9] It is also important in an obstetrical risk factor analysis that inborn delivery room deaths occurring before admission were not excluded and that infants were grouped for comparison according to late death and not neonatal survival or mortality, since postneonatal deaths result primarily from conditions directly related to complications of prematurity.[10]

Among the obstetrical factors, antepartum haemorrhage was associated with an increased mortality similar to that reported in a cohort of more mature infants.[11] The finding of a significant association between maternal hypertension and increased survival may reflect chronic stress in utero, which resulted in fetuses with more mature enzyme systems than expected or who were growth retarded. The association of private health insurance state, use of fetal cardiotocography, and oestriol measurements with increased survival may reflect the standard of obstetric care, although it is more likely that the ability to perform cardiotocography implied a less urgent situation and oestriol measurement might have been indicated for clinically suspected fetal growth retardation. The association between non-vertex presentations with increased mortality in the present series supported previous findings of increased neonatal mortality in breech presentation found in infants over 1000 g.[12]

Previous studies have reported a trend for caesarean section and increased survival in extremely low birthweight infants,[5 7] although others have reported no effect of birth by caesarean section on survival after adjustment for confounding obstetrical factors.[13–15] A definite answer to this controversy can only come from a randomised controlled trial. Variable circumstances were likely to have influenced the decision to deliver by caesarean section or by the vaginal route. It is probably also important to

distinguish caesarean sections that had been carried out before the onset of labour from those that had been carried out during labour. Data on these aspects were unavailable in the present study.

The higher mortality in male compared with female extremely low birthweight infants is probably explained by the slower lung maturation among male fetuses.[16] Small for gestational age infants are obviously more mature for the same birth weight compared with those who are appropriately grown for gestational age in a weight selected population. This accounted for the finding that growth retardation was associated with increased survival in this and another study.[7]

The fact that perinatal asphyxia was associated with increased mortality emphasised the importance of prevention or early detection and treatment of asphyxia in the management of extremely preterm labour.

When all significant perinatal factors were considered in the discriminant function analysis the most important factor associated with increased mortality was clinical evidence of intraventricular haemorrhage. As cerebral ultrasonography was not available for most of the study period probably only the most severe haemorrhages were diagnosed. Large intraventricular haemorrhage with intracerebral extension diagnosed accurately on routine ultrasound has been correlated with increased mortality.[17]

Our analysis of a large number of perinatal factors in normal survivors and those with disability has shown very few significant differences. This poor correlation of disability with perinatal risk factors was also reported in our previous study on an inborn cohort of infants who weighed 1500 g or less[18] and in other studies of extremely low birthweight populations that were predominantly or exclusively outborn.[19–22] Only one previous report had data similar to the present study on perinatal factors associated with disability in an inborn extremely low birthweight population.[7] Significant factors reported have included low Apgar score,[20] mechanical ventilation,[21 22] seizures,[19] and clinical signs of intraventricular haemorrhage. In a recent case controlled study comparing 34 handicapped survivors born at 26–30 weeks' gestation with normal controls epidural anaesthesia, lower maximum oxygen requirement, lower ventilator rate, and absence of intraventricular haemorrhage were associated with normal survival.[23] Intraventricular haemorrhage and seizures were the two most significant perinatal risk factors for disability in the present study. Studies with routine cerebral ultrasound that accurately diagnosed intracerebral extension of intraventricular haemorrhage and periventricular leucomalacia have confirmed that such lesions correlate with poor neurodevelopmental outcome.[24 25] These current methods and other more refined obstetrical and neonatal tools will be required to identify further perinatal risk factors associated with death or disability in this high risk population.

References

1 Yu VYH, Hollingsworth E. Improving prognosis for infants weighing 1000 g or less at birth. *Arch Dis Child* 1980:**55:**422–6.
2 Orgill AA, Astbury J, Bajuk B, Yu VYH. Early development of infants 1000 g or less at birth. *Arch Dis Child* 1982;**57:**823–7.
3 Yu VYH, Hollingsworth E. Respiratory failure in infants weighing 1000 g or less at birth. *Aust Paediatr J* 1979;**15:**152–9.
4 Yu VYH. Treatment for persistent pulmonary hypertension. In: Clinch J, Matthews T, eds. *Perinatal Medicine.* Lancaster: MTP Press Ltd, 1985:189–97.
5 Dillion WP, Egan EA. Aggressive obstetric management in late second-trimester deliveries. *Obstet Gynecol* 1981;**58:**685–90.
6 Herschel M, Kennedy JL, Kayne HL, Henry M, Cetrulo CL. Survival of infants born at 24 to 28 weeks' gestation. *Obstet Gynecol* 1982;**60:**154–8
7 Hoskin EM, Elliot E, Shennan AT, Skidmore MB, Keith E. Outcome of very low-birth weight infants born at a perinatal center. *Am J Obstet Gynecol* 1983;**145:**135–40.
8 Kitchen WH, Campbell NT, Drew JH, Murton LJ, Roy RND, Yu VYH. Provision of perinatal services and survival of extremely low birthweight infants in Victoria. *Med J Aust* 1983;**2:**314–8.
9 Bajuk B, Kitchen WH, Lissenden JV, Yu VYH. Perinatal factors affecting survival of very low birthweight infants—a study from two hospitals. *Aust Paediatr J* 1981;**17:**277–80.
10 Yu VYH, Watkins A, Bajuk B. Neonatal and postneonatal mortality in very low birthweight infants. *Arch Dis Child* 1984;**59:**987–99.
11 Perkins RP. The neonatal significance of selected perinatal events among infants of low birth weight. *Am J Obstet Gynecol* 1981;**139:**546–61.
12 DeCrespigny LJC, Pepperell RJ. Perinatal mortality and morbidity in breech presentation. *Obstet Gynecol* 1979;**153:**141–5.
13 Barrett JM, Boehm FH, Vaughn WK. The effect of type of delivery on neonatal outcome in singleton infants of birth weight of 1000 g or less. *JAMA* 1983;**250:**625–9.
14 Yu VYH, Bajuk B, Cutting D, Orgill AA, Astbury J. Effect of mode of delivery on outcome of very low birthweight infants. *Br J Obstet Gynaecol* 1984;**9:**633–9.
15 Kitchen W, Ford GW, Doyle LW, *et al.* Cesarean section or vaginal delivery at 24 to 28 weeks' gestation: comparison of survival and neonatal and two-year morbidity. *Obstet Gynecol* 1985;**66:**149–57.
16 Khoury MJ, Marks JS, McCarthy BJ, Zaro SM. Factors affecting the sex differential in neonatal mortality: the role of respiratory distress syndrome. *Am J Obstet Gynecol* 1985; **151:**777–82.
17 Szymonowicz W, Yu VYH. Timing and evolution of periventricular haemorrhage in infants 1250 grams or less at birth. *Arch Dis Child* 1984;**59:**7–12.
18 Kitchen WH, Yu VYH, Orgill AA, *et al.* Collaborative study of very low birthweight infants: correlation of handicap with risk factors. *Am J Dis Child* 1983;**137:**555–9.
19 Ruiz MPD, LeFever JA, Hakanson DO, Clark DA, Williams ML. Early development of infants of birth weight less than 1000 grams with reference to mechanical ventilation in newborn period. *Pediatrics* 1981;**68:**330–5.
20 Bennett FC, Robinson NM, Sells CJ. Growth and development of infants weighing less than 800 grams at birth. *Pediatrics* 1983;**71:**319–23.
21 Rothberg AD, Maisels MJ, Bagnato S, Murphy J, Gifford K,

McKinley K. Infants weighing 1000 grams or less at birth: developmental outcome for ventilated and non-ventilated infants. *Pediatrics* 1983;**71**:599–602.

[22] Kraybill EN, Kennedy CA, Teplin SW, Campbell SK. Infants with birth weights less than 1001g. *Am J Dis Child* 1984;**138**: 837–42.

[23] Shennan AT, Milligan JE, Hoskin EM. Perinatal factors associated with death or handicap in very preterm infants. *Am J Obstet Gynecol* 1985;**151**:231–8.

[24] Catto-Smith AG, Yu VYH, Bajuk B, Orgill AA, Astbury J. Effect of neonatal periventricular haemorrhage on neurodevelopmental outcome. *Arch Dis Child* 1985;**60**:8–11.

[25] Szymonowicz W, Yu VYH, Bajuk B, Astbury J. Neurodevelopmental outcome of periventricular haemorrhage and leukomalacia in infants 1250 grams or less at birth. *Early Hum Dev*. (In press.)

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