Improving prognosis for infants weighing 1000 g or less at birth

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SUMMARY In the two years 1977 and 1978, 55 infants weighing ≤ 1000 g were admitted to the neonatal unit of the Queen Victoria Medical Centre. Overall neonatal survival was 60%; 44% of infants weighing 501–750 g and 67% of infants weighing 751–1000 g survived. One postneonatal death occurred at 51 days. Maternal risk factors were present in 80% of infants, although none had an effect on survival. Perinatal asphyxia, as indicated by an Apgar score ≤ 3 at five minutes, and base deficit >10 mmol/l on admission, were associated with decreased survival. Mortality data with increasing postnatal age were used to produce a chart for sequential prediction of neonatal survival. Intraventricular haemorrhage remained the most common necropsy finding. Follow-up of 32 survivors to date has shown no abnormalities, with the exception of one retrolental fibroplasia, and one porencephaly of unknown aetiology. We conclude that the prognosis for infants weighing ≤ 1000 g has continued to improve. From a review of the clinical and pathological characteristics in these infants however, it is obvious that this outcome requires complex organisation and costly resources in perinatal centres to which high-risk pregnancies must be transferred for optimal management both before and after birth.

Advances in perinatal care have resulted in improved management for the mother and fetus during preterm labour and delivery, and for the preterm infant after delivery. The survival rate of infants weighing 1000 g or less at birth has improved only slowly compared with that of more mature preterm infants. These extremely low birthweight (ELBW) infants constitute less than 1% of the newborn population but contribute to 26–51% of neonatal mortality.¹ Because there are so few ELBW infants, it took between 5 and 10 years to obtain adequate data for two surveys,^{1–2} and during that time many aspects of perinatal care had changed.

We review here 55 infants weighing 1000 g or less at birth who were treated at Queen Victoria Medical Centre (QVMC) in the two years 1977 and 1978, during which time neonatal intensive care policies and methods of treatment remained constant. The purpose of this study was to determine the survival rate of this group, the predictive factors for survival,

and the clinical and pathological characteristics of these ELBW infants.

Patients and methods

Study population. Between 1 January 1977 and 31 December 1978, 55 infants whose birthweights were between 501 and 1000 g, were admitted to the neonatal unit at QVMC. 44 (75%) infants were born at QVMC, 13 of whom were from mothers who had emergency transfers to QVMC after preterm labour at other hospitals. These 13 fetuses were delivered within 3 days of 'transfer *in utero*'. The remaining 31 inborn infants were either from booked antenatal patients or from mothers who were referred for management of their high-risk pregnancies and who delivered more than one week after admission. 11 infants were born at other hospitals in the State of Victoria. The Neonatal Emergency Transport Service has been operating in Victoria since October 1976.³

Obstetric and neonatal care. Women in preterm labour were admitted to fetal intensive care, and deliveries of these high-risk pregnancies were attended by a neonatal resuscitation team. The perinatal care and the organisation of neonatal

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services in QVMC have been described by Yu and Wood.⁴ Clinical maturity of the infant was confirmed by the Dubowitz score.⁵ An infant was considered of appropriate weight for gestational age if his birthweight was above the 10th centile of intrauterine growth in a Melbourne population.⁶

Intermittent mandatory ventilation, usually in conjunction with positive end-expiratory pressure, and continuous positive airways pressure were delivered by either nasoendotracheal tube or nasopharyngeal tube, using the Bennett PR11 respirator. Indication for continuous positive airways pressure or intermittent mandatory ventilation was similar to that of Reynolds.⁷ Theophylline was used to facilitate weaning if ventilator dependence seemed to be due to inadequate respiratory effort,⁸ or at the onset of preterm apnoea. Parenteral nutrition was given via peripheral veins and graded down after the start of enteric feeds. Details of the parenteral nutrition regimen, the formulation used, and its administration and monitoring have been reported by Yu *et al.*⁹ Fresh expressed breast milk from the infant's own mother was given whenever possible. Replacement blood transfusions were given in ELBW infants with respiratory distress or preterm apnoea when haematocrit was <40%, when systolic blood pressure was <40 mmHg, or when >10% of the blood volume had been removed for blood tests.¹⁰ Phototherapy was started at a serum indirect bilirubin concentration of 150 $\mu\text{mol/l}$ (8.8 mg/100 ml). Exchange transfusion was carried out if the level reached 200–300 $\mu\text{mol/l}$ (11.7–17.5 mg/100 ml), depending on the presence of risk factors for kernicterus. The parental-care component of the neonatal programme in QVMC¹¹ included an open visiting policy for the extended family, unrestricted contact between parents and their infants, and family-orientated convalescent care.

Follow-up. After discharge each infant was seen regularly by a paediatric consultant who had not taken part in his neonatal intensive care. A Growth and Development Clinic also exists for psychological assessment to complement this follow-up.

Results

Survival rate. 5% of the infants admitted to the neonatal unit in QVMC weighed ≤ 1000 g but they accounted for 22% of the mortality. 33 (60%) of the total 55 ELBW infants survived the neonatal period. One infant died later aged 51 days. The neonatal survival rate was 44% in the 501–750 g group, and 67% in the 751–1000 g group (Table 1). All infants had birthweights which were appropriate for

gestational age. There were 27 boys and 28 girls. Slightly more girls survived (68% compared with 52%). No differences were apparent in survival rates between inborn and outborn ELBW infants (59% v. 64% respectively). Most neonatal deaths were during the first few postnatal days. Information about the survival rates at selected times after birth for the two ranges of birthweights, 501–750 g and 751–1000 g, was used to produce a graph giving the potential for survival (Fig. 1). The prediction of survival at each sequential age gives the outlook for those still living at that time.

Maternal and perinatal risks. 44 (80%) of the 55 ELBW infants were products of high-risk pregnancies. The maternal factors and their frequencies were as follows: maternal age ≥ 35 years (13%), poor reproduction history (gravid ≥ 6 , three consecutive spontaneous abortions, one stillbirth, or one neonatal death) (16%), twin pregnancy (11%), antepartum haemorrhage (29%), pre-eclampsia toxemia (5%), and prolonged rupture of membrane >24 hours before delivery (49%). None of these factors had any effect on survival. The incidence of

Table 1 Neonatal survival rates of infants weighing ≤ 1000 g

Birthweights (g)	Survivors/admissions (% survival)		
	1977	1978	Total
501–750	2/8 (25)	5/8 (63)	7/16 (44)
751–1000	13/21 (62)	13/18 (72)	26/39 (67)
Total	15/29 (52)	18/26 (69)	33/55 (60)

Percentages are given in parentheses.

Fig. 1 Prediction of survival of infants weighing ≤ 1000 g admitted in 1977 and 1978.

Table 2 Perinatal factors in infants weighing ≤ 1000 g

Maternal and perinatal factors	Infants		Survivors	
	No.	(%)	No.	(%)
Mode of delivery				
Vertex	26	(47)	17	(65)
Breech	19	(35)	11	(58)
Caesarean section	10	(18)	5	(50)
Apgar score				
1-2 minutes	24	(44)	14	(58)
{ 0-3			19	(61)
5 minutes	11	(20)	3	(27)
{ 0-3			30	(68)*
Positive pressure resuscitation				
Required	40	(73)	26	(65)
Not required			7	(47)
Acid-base data on admission				
pH	22	(44)	12	(55)
{ < 7.2			20	(71)
Base deficit	13	(26)	4	(31)
{ > 10			28	(76)*
Lowest body temperature (within 3 hours of delivery)				
< 35.5	42	(76)	22	(52)
≥ 35.5			11	(85)

* $P < 0.05$.

perinatal factors and their effect on survival are shown in Table 2. 11 (20%) infants, whose Apgar score at five minutes was 0-3, had a survival rate of 27% compared with 68% survival in those with a score of 4-10 ($\chi^2 = 4.55$, $P < 0.05$). The presence of severe metabolic acidosis, presumably caused by perinatal asphyxia, and defined as a base deficit of more than 10 mmol/l in the first arterial blood sample on admission, was associated with a reduced survival rate ($\chi^2 = 4.57$, $P < 0.05$). Although the survival rate in infants with hypothermia (52%) was lower than in those infants without hypothermia (85%), this difference was not significant ($\chi^2 = 3.06$, $P < 0.1$).

Neonatal events. Table 3 shows the principal diagnoses of these infants. The incidence of hyaline membrane disease (HMD) was 58%; the survival rate was 50% which is not significantly different from those without HMD. The diagnosis of HMD required all the following: respiratory distress not attributable to other causes, chest x-ray showing diffuse granularity, $F_{I_{O_2}} \geq 0.3$ to maintain $P_{a_{O_2}} > 60$ mmHg (7.9 kPa) for at least 3 days after birth, and a maximum $F_{I_{O_2}}$ requirement ≥ 0.4 . The causes and management of respiratory failure and the morbidity from assisted ventilation are reported elsewhere.¹² Pharmacological closure of the patent ductus arteriosus was used successfully as an alternative to surgical ligation.¹³ Phototherapy was required for jaundice in 42 (76%) infants. Exchange transfusions were performed on 9 infants for

Table 3 Principal diagnoses in infants weighing ≤ 1000 g

Diagnosis*	Infants		Survivors	
	No.	(%)	No.	(%)
Hyaline membrane disease	32	(58)	16	(50)
Intrapartum pneumonia	4	(7)	2	(50)
Pulmonary haemorrhage				
without HMD	2	(4)	0	(0)
with HMD	2	(4)	1	(50)
Transient tachypnoea	4	(7)	4	(100)
Wilson-Mikity syndrome	2	(4)	2	(100)
Preterm apnoea				
without lung disease	15	(27)	13	(87)
with lung disease	23	(42)	20	(87)
Patent ductus arteriosus	24	(44)	17	(71)
Jaundice (> 170 μ mol/l)	26	(47)	21	(81)
Necrotising enterocolitis	2	(4)	1	(50)
Septicaemia	3	(5)	1	(30)
Congenital defect	1	(2)	0	(0)

*Many infants had more than one.

hyperbilirubinaemia and on one infant for disseminated intravascular coagulation. 31 (56%) were fed fresh expressed human breast milk from their own mothers. 12 were fed milk formula throughout, and 12 did not receive enteric feeds before death. 41 infants received parenteral nutrition for a duration ranging from 1 to 50 days. Necrotising enterocolitis occurred in only 2 infants, one of whom died from fulminating disease leading to perforation, peritonitis, and death within 11 hours of its onset.

Nursery stay and weight gain. In the survivors, the mean nursery stay was 102 (range 75 to 130) days. They were discharged at a mean postconceptional age of 40.5 (range 37-46) weeks, at a mean discharge weight of 2430 g. In Fig. 2, the nursery weight gain is superimposed on the intrauterine growth chart. Each infant was studied from the week of gestation at

Fig. 2 Nursery weight gain of infants (mean $\pm$ 2 SD) superimposed on intrauterine growth chart of Kitchen.⁶

birth until death, or nursery discharge. Some degree of 'extrauterine growth retardation' was apparent when the nursery growth was compared with that of their intrauterine peers.

Necropsy. Necropsies were performed on 18 of the 23 deaths. The most common diagnoses at necropsy, and presumed causes of death, were intraventricular haemorrhage (65%) and HMD (52%). Coexisting intraventricular haemorrhage and HMD were found in 11 infants. Two infants who developed persistent neurological abnormalities and postintraventricular haemorrhage hydrocephalus, confirmed by brain scanning with computerised axial tomography, had their life-support systems (including mechanical ventilation) withdrawn at 23 and 51 days. Necropsy confirmed severe cerebral destruction and obstructive hydrocephalus.

Follow-up. Retrolental fibroplasia (RLF) was diagnosed in one survivor with neovascularisation and peripheral retinal clouding in one eye and peripheral retinal detachment in the other. Postnatally-acquired cytomegalovirus (CMV) infection was diagnosed in 4 infants when each was 2 months. The infants were probably infected from their multiple replacement blood transfusions. One of the CMV excretors had excessive increase in head circumference from age 5 weeks, which investigations showed was due to porencephaly. Cholestatic jaundice developed after prolonged parenteral nutrition in 2 infants, but this had resolved at 4 months. Although the 32 survivors, 3 months to 2 years after birth, were too young for accurate estimates of development and intellectual function, none was suspected to have any major handicap except for the one with RLF and the one with porencephaly.

Discussion

Survival rates from earlier studies of ELBW infants are given in Table 4. There has been a gradual but noticeable increase in survival rate during the last 15 years. Although it is accepted that an ELBW infant is at an additional risk if delivered in a hospital that has not the appropriate perinatal facilities or if he has to be taken to a neonatal intensive care unit, it was not surprising that the survival rate of inborn and outborn infants was similar, as babies in the latter group were probably selected for referral because they were in relatively good condition and represent only those infants deemed 'capable of survival'.

Although 80% of mothers in this series could have been recognised early as high-risk, the maternal factors alone had no significant effect on survival.

Table 4 Survival rates in other series of infants weighing ≤ 1000 g

Authors	Range of birth dates	Range of birthweights (g)	Neonatal survivors	
			No.	%
Alden <i>et al.</i> ¹ n=161	1965-70	400-999	22	14
Grassy <i>et al.</i> ¹⁷ n=98	1968-72	680-1000	28	29
Stewart <i>et al.</i> ² n=148	1966-75	500-1000	48	32
Pape <i>et al.</i> ¹⁴ n=97	1974	590-1000	46	47
Kopelman ¹⁸ n=43	1975-76	Not known	18	42
Present study, n=55	1977-78	510-1000	33	60

The one factor that influenced survival was perinatal asphyxia, as assessed by the 5-minute Apgar score and acid-base status on admission. This finding was the same as that previously reported for infants weighing ≤ 1500 g.⁴ Improved methods for the management of HMD might have resulted in a survival rate for HMD which was not significantly different from those infants without HMD (50% v. 74%). This finding was different from that in one earlier series² but supports a similar finding in a study with a more recent cohort.¹⁴ Delivery by caesarean section has been reported to be a favourable factor influencing survival.² Differences in survival in relation to mode of delivery were however not obvious in this series.

The incidence of patent ductus arteriosus reported by Pape *et al.*¹⁴ and that of jaundice reported by Stewart *et al.*² were slightly lower than in our series. This may be because more infants are now surviving, thus allowing for the development of such conditions in the early neonatal period. Necrotising enterocolitis was rare in these ELBW infants compared with some centres in North America.¹⁵ The prevalence of this disease is known to vary greatly between countries and between regions. The use of parenteral nutrition allowed for more normal postnatal growth during this critical phase of development. However, hyperglycaemia has become a significant metabolic complication with such an aggressive nutritional programme.¹⁶

One of the most difficult questions to answer concerns the chance of survival. Parents of ELBW infants naturally ask about the probability of survival, and medical or nursing staff have great difficulty in dealing with this inquiry. Mortality data with increasing postnatal age can usefully be applied to predict survival. It is useful for each neonatal intensive care unit to prepare similar charts from its own experience with regular updating. It is not suggested that parents be spontaneously informed of the probability of survival, but the medical and nursing staff are more likely to be effective in caring for the parents if they know the likely outcome and use the information with discretion.

The results of this series are encouraging for neonatal survival in ELBW infants. Although the quality of survival of this group of ELBW infants cannot yet be accurately ascertained, the good prognosis for infants with equally low birthweights has been shown by Stewart *et al.*² where only 7% of the survivors had major handicaps and 15% had minor ones. Although our policy is to provide optimal care for all infants of 24 weeks' gestation or more, our current ethical guidelines are similar to those of Stewart *et al.*² in that when an infant develops a persistent neurological abnormality—such as after a large intraventricular haemorrhage—which would make survival unlikely and major handicap virtually certain, intensive life-support systems are withdrawn after discussion with the parents and medical and nursing staff, as was the case in two infants in this series.

Because less than 1% of liveborn infants weigh ≤ 1000 g or less at birth and because they develop multiple potentially lethal or damaging perinatal problems, we should be ready and able to transfer these high-risk pregnancies to perinatal centres to allow for optimal care both before and after birth. Failing this, the newborn should be transferred to a neonatal intensive care unit by a specialised neonatal transport service, a facility which has become accepted as an important and integral part of comprehensive perinatal care. Excellent outcomes for these infants are possible, but they require complex organisation, costly resources, and hard work.

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