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Factors Affecting Short-Term Mortality in Very Low Birth Weight Infants in Japan

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Oshiki, R., Nakamura, K., Yamazaki, A., Sakano, C., Nagayama, Y., Ooishi, M. and Yamamoto, M. *Factors Affecting Short-Term Mortality in Very Low Birth Weight Infants in Japan*. Tohoku J. Exp. Med., 2005, **205** (2), 141-150 —— No epidemiological surveys have examined risk factors related to the death of very low birth weight infants (VLBWIs) in Japan. The objectives of this study were to examine the death rate and fatalities related to complications among VLBWIs, and to analyze factors possibly determining the death of VLBWIs. The subjects of this study were 811 VLBWIs admitted to the Neonatal Care Center of Niigata City General Hospital between April 1987 and March 2003. We obtained information on gender, birth weight, gestational age, Apgar scores, single/multiple pregnancy, postnatal transfer, mode of delivery, complications and outcome (alive or deceased) at the time of discharge from medical records. Of the 811 infants, 98 died prior to discharge (12.1%). Logistic regression analysis showed that independent risk factors for death of VLBWIs were male gender (relative risk [RR]: 2.0), low birth weight (RR: 0.56), necrotizing enterocolitis (RR: 58.0), pulmonary hypoplasia (RR: 37.8), chromosomal abnormalities (RR: 36.3), congenital heart diseases (RR: 9.8), persistent fetal circulation (RR: 9.6), neonatal asphyxia (RR: 6.3) and sepsis (RR: 4.4). The risk for death rises 1.8-fold if birth weight decreases by 100 g. A very high risk of perinatal death is associated with necrotizing enterocolitis, pulmonary hypoplasia or chromosomal abnormalities. The risk of death due to congenital heart diseases or neonatal asphyxia is relatively lower, but the incidences of these two disorders are high (8% and 6%, respectively). From the viewpoint of prophylactic treatment aimed at reducing the death rate of VLBWIs, measures to increase birth weight are of primary importance. Furthermore, early treatment and improved perinatal management of congenital heart diseases and neonatal asphyxia are anticipated to reduce the overall death rate of VLBWIs. ———— very low birth weight infant (VLBWI); mortality; birth weight; risk factor; historical cohort study

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The number of very low birth weight infants (VLBWIs), defined as an infant weighing less than 1,500 g at birth, has been increasing. The percentage of VLBWIs among all newborns in Japan has been rising, from 0.3% in 1960, to 0.4% in 1980 and 0.7% in 2002 (Mother's and Children's Health and Welfare Association 2004). Major factors explaining the increase in the number of VLBWIs are: (1) an increase in the total number of pregnancies and labors due to advances in infertility treatment and (2) improved neonatal care following introduction of surfactant therapy, assisted ventilation, and other modern medical technologies (Dina et al. 2000).

As compared to mature infants, VLBWIs are more likely to develop complications and have a higher death rate because of immaturity of respiratory, cardiovascular and metabolic functions, as well as lower resistance to exogenous bacteria. Several factors associated with the high death rate of VLBWIs have been identified. These factors include complications, male gender (Stevenson et al. 2000), low birth weight or gestational age at birth (Ho and Malaysian Very Low Birth Weight Study Group 2001) and certain modes of delivery (Cibils et al. 1994; Paul et al. 2002). Factors recognized as being closely related to the death of VLBWIs include congenital abnormalities, neonatal asphyxia, and infection (Richard 2004). In addition, non-host factors (the neonatal management capacities of a given medical facility, postnatal transport of the infant to a medical facility) have also been recognized as possibly being related to the death of VLBWIs. To date, however, few well-designed epidemiological surveys have examined risk factors related to the death of VLBWIs, and no such study has been conducted in Japan.

The first objective of this study was to examine the death rate and fatalities related to complications among VLBWIs. The second objective was to analyze factors possibly determining the death of VLBWIs, including gender, birth weight, gestational age, mode of delivery and complications. By analyzing all clinical data collected on VLBWIs managed during the 16-year period at a medical facility serving as the core center for critical neonatal care in a district, this report will focus on measures aimed at reducing the death rate of VLBWIs.

Materials and Methods

The subjects of this study were 821 VLBWIs born at the Niigata City General Hospital or other facilities between April 1987 and March 2003 and admitted to the Neonatal Care Center of Niigata City General Hospital. Of these infants, 10 for whom data on complications were not available were excluded from the analysis. Thus, 811 infants were included in the final analysis. The Neonatal Care Center of Niigata City General Hospital was founded in April, 1987, and was until recently the only neonatal care center in Niigata Prefecture. During the subsequent 11-year-period until 1997, the majority of infants with health problems received medical care at this center. In 1998, another neonatal care center was opened in Niigata Prefecture. Since that time, the Neonatal Care Center of Niigata City General Hospital has served primarily Niigata City, its suburbs, Sado district and the northern part of Niigata Prefecture (covering about 2/3 of births in Niigata Prefecture). This study was authorized by the Ethics Committee of Niigata City General Hospital.

The following types of information were derived from medical records, prepared by attending physicians, of individual infants: gender, birth weight, gestational age, Apgar scores (at 1 and 5 minutes), single/multiple pregnancy, postnatal transfer (coded as 0: born in Niigata City General Hospital [birth within], 1: born at other hospitals and transported after birth [neonatal transfer]), mode of delivery (0: vaginal, 1: cesarean section), blood transfusion, complications and outcome (alive or deceased) at the time of discharge. In the present study, infants that died during hospitalization were counted as deceased, and infants discharged alive were counted as survivors ("short-term" mortality is calculated based on this definition). Major complications determining the survival or death of infants were classified into respiratory diseases, circulatory diseases, gastrointestinal diseases, central nervous system (CNS) diseases, infections, blood diseases, congenital abnormalities and others. Respiratory diseases were subdivided into pulmonary hypoplasia, pulmonary hemorrhage, meconium aspiration syndrome, respiratory distress syndrome and chronic lung diseases. Wilson-Mikity syndrome was also considered to be a chronic lung disease. Circulatory diseases included congenital heart diseases (congenital heart dis-

eases [CHDs]: ventricular septal defect, atrial septal defect, tetralogy of Fallot, and others), neonatal asphyxia, persistent fetal circulation, twin-to-twin transfusion syndrome (TTTS) and patent ductus arteriosus. Gastrointestinal diseases included necrotizing enterocolitis (NEC), gastrointestinal perforation and Hirschsprung disease. CNS diseases included hydrocephalus, intracranial hemorrhage (including bleeding within the skull and intraventricular hemorrhage), hypoxic ischemic encephalopathy and periventricular leukomalacia. Infections included sepsis and meningitis. Blood diseases included disseminated intravascular coagulation, thrombocytopenia and polycythemia. Congenital abnormalities included chromosomal abnormalities (including trisomies 21, 18 and 13) and malformation syndromes (Pierre-Robin syndrome, Cornelia de Lange syndrome, and other multiple malformations). A diagnosis of neonatal asphyxia was made if the one-minute Apgar score was below 6.

In bivariate analyses, Student's *t*-test or the Wilcoxon rank-sum test was used for testing differences in continuous variables between two groups, and Fisher's exact test was employed to assess the difference in death rate between the two groups. Independent risk factors associated with death were identified by step-wise logistic regression analysis, with death serving as an outcome variable. The following variables were analyzed as possible predictors: basic variables (gender, gestational age, birth weight, Apgar score, single/multiple pregnancy, postnatal transfer, and cesarean section) and complications identified in the bivariate analysis as being significantly related to death. The statistical analysis package Release 8.02 (SAS) was used for all statistical analyses. $P < 0.05$ was regarded as indicating a statistically significant difference.

Results

Of the 811 infants, 98 died prior to discharge, with the death rate being 12.1%. Fig. 1 presents annual death rates. The death rate varies markedly among years, ranging from 21.0% in 1993 to 3.2% in 2002. The small sample size in each year may have yielded such unstable death rates. During the 15-year period, the death rate tended to decrease but this trend was not statistically significant ($p = 0.2317$).

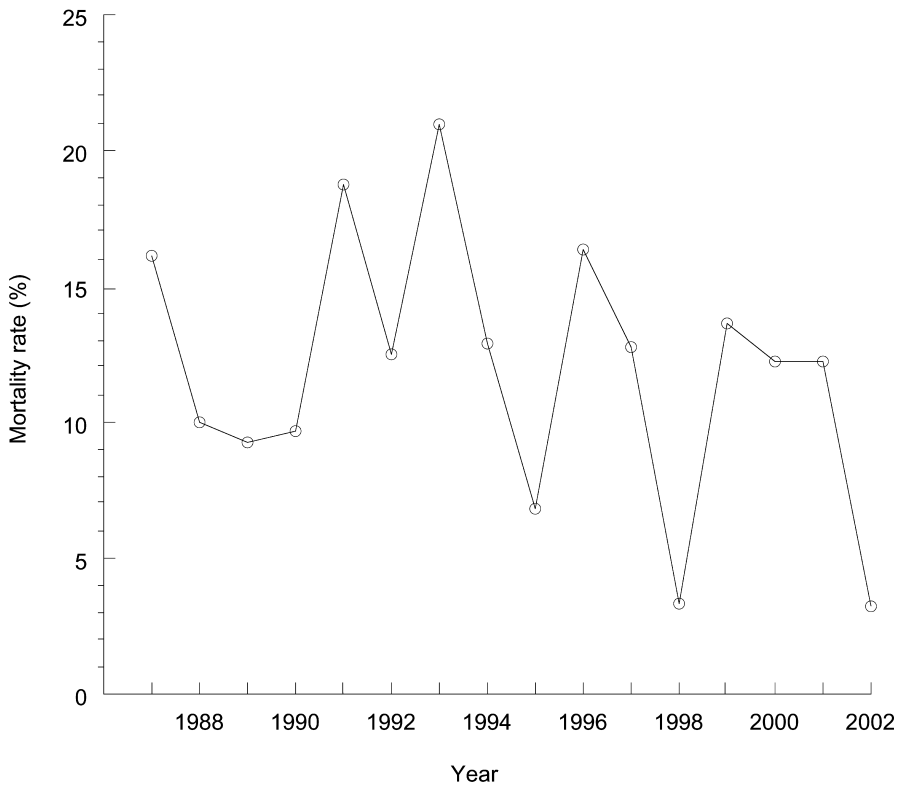

Fig. 1. Annual changes in mortality rates of very low birth weight infants.

TABLE 1. *Numbers of subjects and deaths classified by sex, pregnancy, delivery, 1-min. and 5-min. Apgar score levels, and the presence of postnatal transfer*

	Number of subjects	Number of death (%)	p value*
Sex			
Male	424	56 (13.2)	
Female	387	42 (10.9)	0.3324
Pregnancy			
Single	620	80 (12.9)	
Multiple	191	18 (9.4)	0.2526
Mode of delivery[a]			
Caesarean section	291	40 (13.8)	
Vaginal delivery	498	52 (10.4)	0.1691
1-min Apgar score[b]			
≧ 8 (normal)	232	12 (5.2)	
< 8	554	77 (13.9)	0.0003
5-min Apgar score[c]			
≧ 8 (normal)	466	23 (4.9)	
< 8	271	57 (21.0)	< 0.0001
Postnatal transfer[d]			
Present	161	18 (11.7)	
Absent	623	73 (11.0)	1.0000

*Fisher's exact test
Not available were data for 22 subjects ([a]), 25 subjects ([b]), 74 subjects ([c]), and 27 subjects ([d]).

Table 1 shows the total number of infants and the number of deceased infants in relation to gender, single/multiple pregnancy, cesarean section, Apgar score and postnatal transfer. None of these variables differed significantly between the survivor and the deceased groups, except for the 1-min and 5-min Apgar score levels. Infants with low levels of 1-min and 5-min Apgar score (< 8) had a significantly higher death rate than those with normal levels (≧ 8).

Table 2 shows the death rate by gestational age and birth weight. Death rates were higher for infants born at a gestational age below 26 weeks and those with a birth weight of less than 750 g. Gestational age (mean ± S.D.) at the time of birth differed significantly between the survivor group (206.7 ± 19.9 days) and the deceased group (195.2 ± 24.8 days) ($p < 0.0001$). The birth weight (mean ± S.D.) differed significantly between the survivor group (1122 ± 245 g) and the deceased group (867

TABLE 2. *Death rates according to gestational age and birth weight*

	Death rate (%)
Gestational age (week)	
22-25	35/106 (33.0)
26-29	35/384 (9.1)
30-33	21/260 (8.1)
34-37	6/60 (10.0)
38 ≦	1/1* (100.0)
Birth weight (g)	
< 500 g	7/9 (77.8)
500-749.9	32/90 (35.6)
750-999.9	28/203 (13.8)
1000-1249.9	19/242 (7.9)
1250 ≦	12/267 (4.5)

*The dead infant had multiple complications, including 18-trisomy, neonatal asphyxia, ventricular and atrial septal defects.

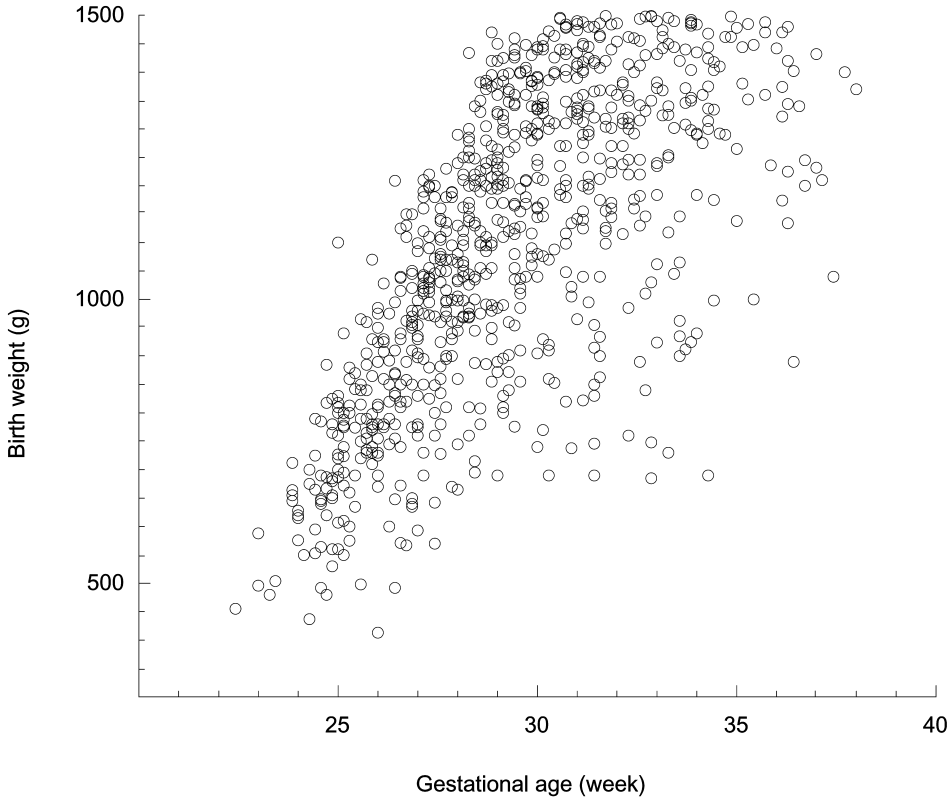

Fig. 2. Association between gestational age and birth weight. The correlation coefficient is 0.68 ($p <$ 0.0001).

± 273 g) ($p < 0.0001$). Fig. 2 shows the relationship between gestational age at birth and birth weight. The coefficient of correlation between these two variables was 0.68 ($p < 0.0001$).

Table 3 shows the death rate in relation to complications, the cumulative incidence of complications and the presence/absence of complications. Complications associated with a significantly increased fatality rate were pulmonary hypoplasia, pulmonary hemorrhage, CHDs, persistent fetal circulation, patent ductus arteriosus, NEC, gastrointestinal perforation, neonatal asphyxia, hydrocephalus, intracranial hemorrhage, sepsis, meningitis, disseminated intravascular coagulation, chromosomal abnormalities and malformation syndrome.

When performing logistic regression analysis, the following complications were included in the regression model as possible predictors: pulmonary hemorrhage, CHDs, persistent fetal circulation, patent ductus arteriosus, NEC, gastrointestinal perforation, neonatal asphyxia, hydrocephalus, intracranial hemorrhage, sepsis, meningitis, disseminated intravascular coagulation, chromosomal abnormalities and malformation syndromes. By the step-wise method, birth weight, gender and seven disorders (NEC, pulmonary hypoplasia, chromosomal abnormalities, sepsis, neonatal asphyxia, persistent fetal circulation and CHDs) were identified as significant variables (Table 4). Table 4 shows the relative risk (RR) after adjustment for confounding variables. The contributions of the seven disorders, selected as independent variables, to the death rate of the entire population, were analyzed by calculating the population attributable risk percent (PAR %) from the data shown in Table 3. PAR%, thus calculated, was 13.5% for NEC, 8.7% for chromosomal abnormalities, 19.5% for sepsis, 16.4% for neonatal asphyxia, 4.4% for persistent fetal circulation and 33.4% for CHDs.

TABLE 3. *Cumulative incidence of each complication, and comparison of death rates between infants with and without each complication*

Complication	Cumulative incidence (%)	Death rate (%) in infants		p value[†]
		with complication	without complication[*]	
Respiratory diseases				
Pulmonary hypoplasia	1.1	7/9 (77.8)	91/802 (11.4)	< 0.001
Pulmonary hemorrhage	2.3	10/19 (52.6)	88/792 (11.1)	< 0.001
Meconium aspiration syndrome	1.2	2/10 (20.0)	96/801 (12.0)	0.345
Respiratory distress syndrome	37.2	42/302 (13.9)	56/509 (11.0)	0.222
Chronic lung diseases	19.0	16/154 (10.4)	82/657 (12.5)	0.583
Circulatory diseases				
Congenital heart diseases	8.0	38/65 (58.5)	60/746 (8.0)	< 0.001
Neonatal asphyxia	6.0	21/49 (42.9)	77/762 (10.1)	< 0.001
Persistent fetal circulation	1.8	6/15 (40.0)	92/796 (11.6)	0.005
TTTS	1.2	2/10 (20.0)	96/801 (12.0)	0.345
Patent ductus arteriosus	21.9	35/178 (19.7)	63/633 (10.0)	< 0.001
Gastrointestinal diseases				
Necrotizing enterocolitis	2.1	15/17 (88.2)	83/794 (10.5)	< 0.001
Gastrointestinal perforation	0.7	3/6 (50.0)	95/805 (11.8)	0.026
Hirschsprung disease	0.3	1/3 (33.3)	97/808 (12.0)	0.321
Central nervous system disorders				
Hydrocephalus	2.0	6/16 (37.5)	92/795 (11.6)	0.008
Intracranial hemorrhage	5.7	16/46 (34.8)	82/765 (10.7)	< 0.001
HIE	0.5	1/4 (25.0)	97/807 (12.0)	0.403
Periventricular leukomalacia	2.6	0/21 (0.0)	98/790 (12.4)	0.096
Infectious diseases				
Sepsis	3.7	22/30 (73.3)	76/781 (9.7)	< 0.001
Meningitis	0.9	3/7 (42.9)	95/804 (11.8)	0.042
Blood diseases				
DIC	3.8	24/31 (77.2)	74/780 (9.5)	< 0.001
Thrombocytopenia	1.0	0/8 (0.0)	98/803 (12.2)	0.606
Polycythemia	0.4	0/3 (0.0)	98/808 (12.1)	1.000
Congenital abnormalities				
Chromosomal abnormalities	1.6	10/13 (76.9)	88/798 (11.0)	< 0.001
Malformation syndromes	1.5	6/12 (50.0)	92/799 (11.5)	< 0.001
Others				
Liver diseases	1.4	1/11 (9.1)	97/800 (12.1)	1.000

TTTS, twin-to-twin transfusion syndrome; HIE, hypoxic ischemic encephalopathy; DIC, disseminated intravascular coagulation.

[*]Subjects without the complication concerned are included in the denominator.

[†]Fisher's exact test.

TABLE 4. *Variables predicting death in very low birth weight infants, selected by the stepwise logistic regression method*

Predictors	Adjusted relative risk	95% confidence interval
Necrotizing enterocolitis	58.0	9.3-360.4
Pulmonary hypoplasia	37.8	6.4-221.5
Chromosomal abnormalities	36.3	6.0-221.4
Congenital heart diseases	9.8	3.9-24.9
Persistent fetal circulation	9.6	2.1-45.2
Neonatal asphyxia	6.3	2.5-15.7
Sepsis	4.4	1.2-15.7
Sex (Female, 0; male, 1)	2.0	1.0-4.0
Birth weight (100 g)	0.56	0.47-0.70

DISCUSSION

In this study, the death rate for the 811 VLBWIs was 12.1%. The death rate for VLBWIs reported from other facilities ranged from 9.5 to 27% (Lagercrantz et al. 1997; Yeo et al. 1997; Chye and Lim 1999; Grupo Colaborativo Neocosur 2002; Stranak et al. 2002). Simple comparison among these death rates is not possible, in view of possible differences in therapeutic skill among different countries or facilities. Furthermore, the infants surveyed do not always represent the entire VLBWI population. That is, selection bias cannot be ruled out. In Niigata Prefecture, the neonatal death rate was 1.9/1000 and the infant death rate was 3.4/1000 in 1990. These rates were lower than those of any other prefecture in Japan, suggesting that the highest level of perinatal care in Japan had been provided in Niigata Prefecture (Mother's and Children's Health and Welfare Association 2004). Since the present study was conducted at only one facility (a neonatal care center providing high-level services), it is reasonable to assume that differences in care among the infants and subject selection bias were minimal. This can be viewed as the greatest advantage of the present study.

Gestational age at birth and birth weight are closely related to the degree of organ maturity. These variables are considered to be major factors determining the survival of VLBWIs (Bernstein et al. 2000; Ho and Malaysian Very Low Birth Weight Study Group 2001). In the present study, birth weight was identified as a variable better predicting the death of infants than the gestational age at birth. That is, the death rate rose as the birth weight decreased. Logistic regression analysis allowed birth weight to be identified as a significant independent variable. The logistic regression analysis results indicate that the risk for death rises approximately 1.8-fold as the birth weight of VLBWIs decreases by 100 g. The correlation between gestational age and death was weaker than that between birth weight and death. This may be explained as follows. Delivery of a VLBWI is often preceded by poor intrauterine growth, and, as shown in Fig. 2, a fetus staying in the uterus for a longer time will not necessarily have a higher birth weight or be born in a condition more favorable for survival.

In the logistic regression analysis, the death rate for male VLBWIs was twice that for female VLBWIs. In all previous studies dealing with the relationship between gender and death of VLBWIs, the death rate was higher for boys (Lagercrantz et al. 1997; Stevenson et al. 2000), consistent with the observations of the present study. This finding appears to be associated with maturation of organs such as the lungs being slower in boys than in girls. In fact, it has been reported that boys are more likely to develop respiratory insufficiency or cerebral complications (Stevenson et al. 2000).

Of the diseases developing in VLBWIs, NEC was found to be associated with the highest risk of death (adjusted RR: 58.0). This is a representative intractable disease seen in VLBWIs. The VLBWI death rate from NEC is reportedly 39-50% (Mogilner and Shanon 1983; Narang et al. 1993). Low birth weight and gestational age are considered to further raise the death rate from NEC (Narang et al. 1993). In the present study of

VLBWIs, the death rate for infants with NEC was very high (88.2%). At present, it appears to be difficult to save the lives of VLBWIs with NEC.

Pulmonary hypoplasia was also identified as a factor associated with a high risk of death for VLBWIs (adjusted RR: 37.8). Pulmonary hypoplasia involves disturbed lung growth and is often seen in VLBWIs. It is difficult to save the lives of infants with this condition. No lung disease other than pulmonary hypoplasia was found to markedly increase the risk of death in VLBWIs.

In addition to the two diseases mentioned above, chromosomal abnormalities were found to be associated with a high risk of death in VLBWIs (adjusted RR: 36.3). Infants with chromosomal abnormalities often have low body weights for their gestational age at birth (Kirkinen et al. 1983), and chromosomal abnormality has been considered to increase the risk of death in VLBWIs (Powell et al. 1988). Various chromosomal abnormalities were observed in our VLBWIs, including 5 cases of trisomy 21, 6 of trisomy 18, one with trisomy 13 and one with 7q-trisomy. Numbers of cases are not sufficient to calculate the death rates for each of these chromosomal abnormalities.

Among circulatory diseases, the following were identified as independent risk factors for death of VLBWIs: CHD (adjusted RR: 9.8), persistent fatal circulation (adjusted RR: 9.6) and neonatal asphyxia (adjusted RR: 6.3). Heart failure due to various factors is often a problem for infants with CHD, and hypoxemia due to right-to-left shunting is a common problem for infants with persistent fatal circulation (Tamura et al. 1997). Kecskes and Cartwright (2002) reported the death rate of VLBWIs from CHD to be 40.4%. In the present study, the death rate from CHD was 58.5%. The cumulative incidence of CHD was as high as 8%, and had the highest PAR% (33.4%) among the complications observed in VLBWIs. Appropriate management of CHD is expected to contribute greatly to reducing the overall death rate of VLBWIs. In recent years, it has become possible to perform gene diagnosis at the molecular level and ultrasound diagnosis of fetal abnormalities. The death rate from CHD will be reduced by early treatment, beginning immediately after birth. Neonatal asphyxia is known to be particularly likely to develop in low birth weight infants, and certain maternal factors influence its development. Even when the lives of infants with severe neonatal asphyxia can be saved, sequelae such as cerebral palsy are not uncommon (Thornberg et al. 1995). In addition to the immaturity of affected infants, maternal factors (toxemia of pregnancy, diabetes mellitus) can also play important roles in the onset of neonatal asphyxia. Improvement in the management of these conditions and related factors may allow prevention of neonatal asphyxia.

In the present study, sepsis was identified as a factor independently associated with the death of VLBWIs (adjusted RR: 4.4). Sepsis in neonates can be divided into an early onset type (within 3 days of birth) and a delayed onset type (4 or more days after birth). The death rate is considered to be higher for the early than for the delayed onset type. Among VLBWIs, the incidence of early onset type sepsis and the associated death rate are reportedly 1.5% and 37%, respectively (Stoll et al. 2002). According to a study carried out in Israel (Makhoul et al. 2002), the incidence of delayed onset type sepsis among VLBWIs was 30% and the death rate was 16.9%. The data collected in the present study do not distinguish the early from the delayed onset type, making it impossible for us to compare the data from the present study with those reported in the literature. In the present study, the unadjusted death rate from sepsis (73.3%) and the unadjusted RR (7.5) initially appeared high. However, the odds ratio after adjustment for other factors was low (4.4). This indicates that the apparent death rate from sepsis was high due to complications of sepsis with other serious diseases. Considering that at our neonatal care center state-of-the-art measures are employed to prevent infections, it is reasonable to assume that infections were severe and intractable in the fatal cases.

Several previous studies have examined the relationship of the mode of delivery (among others cesarean section) to the survival of VLBWIs. Some investigators assert that cesarean section

would be safer for extremely low birth weight infants without complications (Bottoms et al. 1997). However, cesarean section involves the risk of sepsis due to operative infection (Leeuw et al. 2002; Makhoul et al. 2002). Therefore, cesarean section may not necessarily be useful in reducing the death rate of such infants. Neither the present nor previous studies (Leeuw et al. 2002; Paul et al. 2002) found a correlation between cesarean section and the death rate. No significant difference in death rate was observed between infants born at our hospital and infants born at other facilities and transferred to our center after birth, and the relation between single/multiple pregnancy and death rate is also unclear (Lagercrantz et al. 1997; Donnovan et al. 1998). Additional studies are needed to reach conclusions on these issues.

In conclusion, a very high risk of perinatal death in VLBWIs is associated with NEC, pulmonary hypoplasia or chromosomal abnormalities. Although the risk of death due to CHD and neonatal asphyxia is lower than the risk associated with each of the three diseases mentioned above, the incidences of these two disorders are relatively high. Therefore, early treatment and improved perinatal management of CHD and neonatal asphyxia may reduce the overall death rate of VLBWIs. In the future, it would be desirable to comprehensively evaluate the survival (including sequelae) of VLBWIs, from not only the clinical standpoint but also in terms of quality of life (QOL).

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