Population-based Study of Chronic Lung Disease in Very Low Birth Weight Infants in North Carolina in 1994 With Comparisons With 1984

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ABSTRACT. ***Objective.*** **To assess the pulmonary outcomes of very low birth weight (VLBW) infants in North Carolina in 1994 and to compare rates of survival and chronic lung disease (CLD) between 1994 and 1984 (see reference 2).**

Methods. **Data were collected prospectively by collaborators from all 13 neonatal intensive care units in North Carolina to determine survival and pulmonary outcomes of infants with birth weights of 500 to 1500 g. State vital statistics data were used to confirm completeness of the sample. CLD was defined as oxygen or ventilator therapy at 36 weeks' postmenstrual age (PMA). For comparisons with the 1984 cohort, survival and pulmonary outcomes of infants defined to be at risk for CLD (ventilated >48 hours and survived 30 days) were recorded at 30 days, 3 months, and 6 months of postnatal age.**

Results. **Outcome data were available for 1413 (92%) of the in-state VLBW live births. Of VLBW infants, 224 (15%) died before 48 hours of age. The overall rate of CLD in 1994 at 36 weeks' PMA was 25%. Rates by birth weight group were 57% for 500 to 750 g birth weight (BW), 41% for 751 to 1000 g BW, 19% for 1001 to 1250 g BW, and 8% for 1251 to 1500 g BW. Infants who received ventilator therapy for >48 hours accounted for 89% of the CLD cases. The CLD rate at 36 weeks' PMA in infants weighing 751 to 1500 g was 37% for those ventilated >48 hours versus 5% for those ventilated <48 hours (OR: 7.1; 95% CI: 4.4–11.3). Overall survival in 1994 was significantly higher for infants than in 1984 (78% vs 74%), most notably in infants 500 to 750 g BW (37% vs 24%), and 751 to 1000 g BW (82% vs 65%). When compared with 1984, the CLD rates in those infants defined to be at risk were significantly higher in 1994 at 30 days (68% vs 54%) and at 3 months (24% vs 15%) of postnatal age. For at-risk infants in 1994, there were fewer infants on the ventilator, but more infants on oxygen alone at all measured time points compared with 1984.**

Conclusion. **Survival of VLBW infants has improved since 1984. Ventilator therapy for >48 hours remains a significant risk factor for CLD. The incidence of CLD has increased from 1984 to 1994 but has shifted from ventilator to oxygen therapy.** ***Pediatrics*** **1999;104(2). URL: http://www.pediatrics.org/cgi/content/full/104/2/e17;** ***bronchopulmonary dysplasia, epidemiology, infant, low birth weight, intensive care units, neonatal statistics, infant mortality, prospective studies.***

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ABBREVIATIONS. VLBW, very low birth weight; CLD, chronic lung disease; NICU, neonatal intensive care unit; PMA, postmenstrual age.

The incidence of very low birth weight (VLBW) births remains an important public health concern in the United States. In 1994, 1.3% of all infants born in the United States weighed <1500 g at birth.[1] Collectively, disorders relating to short gestation represent the second leading cause of infant mortality, accounting for 13% of all infant deaths in the United States in 1994 and 1995.[1] VLBW infants often require complex, lengthy, and costly medical management. In addition, these infants experience multiple morbidities, the most common being infantile chronic lung disease (CLD). Kraybill et al[2] reported the incidence of CLD in 1984 from a population-based study of VLBW infants in North Carolina. This study defined an at-risk population as those who received assisted ventilation for >48 hours and who had survived 30 days. The CLD rate for these at-risk VLBW infants at 30 days of age was 54%. Recent studies in the postsurfactant era have reported 30-day CLD rates of 27%,[3] 31%,[4] and 6%.[5] These multicenter studies reported outcomes for all VLBW infants admitted to participating neonatal intensive care units (NICUs) rather than for a defined at-risk population. The data of Palta et al[3] suggested an increase in CLD from the presurfactant to postsurfactant period, but survival without CLD morbidity did not change.

We performed a population-based study of VLBW infants in North Carolina to determine survival and rates of CLD. To identify the impact of perinatal and neonatal therapies introduced in the past decade, changes in outcomes were investigated by comparing these results with the study conducted by Kraybill et al.[2]

METHODS

The 13 NICUs in North Carolina that routinely manage VLBW infants participated in the study. The outcomes of VLBW infants with birth weights between 500 and 1500 g born during the period beginning January 1, 1994, and ending December 31, 1994, who survived >48 hours were investigated. The outcomes of infants with birth weights <500 g were not investigated, because they are not provided intensive care routinely and they rarely survive. Both inborn and outborn infants cared for at a participating center were included in the study. In this report, the term VLBW refers to infants with birth weights 500 to 1500 g.

The total number of live births in North Carolina in 1994 and the birth weight distribution of all VLBW infants were obtained from the North Carolina State Center for Health Statistics. State vital statistics data were also used to identify the number and birth weight distribution of all neonatal deaths at <48 hours of age as well as the number of multiple births and fetal deaths.

Study data were collected prospectively through a questionnaire distributed to collaborators at each center. The questionnaire was constructed to obtain basic demographics, survival data, and pulmonary outcome for each infant. When necessary, retrospective chart reviews were performed to obtain missing data. Completed data sheets were sent to a central site and entered into a commercial database (EpiInfo, Centers for Disease Control and Prevention, Atlanta, GA).

Gestational age was calculated based on obstetric expected due dates if the mother's dates were consistent with obstetric examinations during pregnancy. Alternatively, for inconsistent dates, the Ballard examination was used.

The rate of CLD in 1994 was calculated using the definition of treatment with supplemental oxygen or ventilator therapy at 36 weeks' postmenstrual age (PMA).

For the purpose of comparison with the 1984 North Carolina cohort,[2] the group of infants believed to be at risk for CLD was defined as those infants who received mechanical ventilation for ≥48 hours and who survived to ≥30 days of age. Similarly, for this at-risk group, supplemental oxygen and ventilator therapy were noted at 30 days, 3 months, and 6 months of postnatal age, and CLD rates at each time point were calculated using the number of at-risk infants as the denominator. Infants discharged from the NICU without supplemental oxygen therapy before 3 months of age were considered to be independent of the need for supplemental oxygen at 3 and 6 months. For infants who were receiving supplemental oxygen when discharged from a participating center to home or to a community hospital, follow-up data were obtained from the infant's local care provider. Survival was defined as being alive at discharge to home or at 6 months of age if still hospitalized (also referred to as in-hospital survival).

Population differences were tested using the χ^2 analysis and Fisher's exact test. Probability levels <.05 were considered significant. Relative risks (RRs) and 95% CIs were calculated using EpiInfo software.

RESULTS

Study Population

In 1994, there were 1570 live births to North Carolina residents with birth weights between 500 and 1500 g. A total of 30 infants were delivered out-of-state. Of the remaining 1540 infants cared for in North Carolina nurseries, there were 60 for whom only the birth weight was known. For 67 infants, survival outcome, but not pulmonary outcome, was known, therefore survival data were available for 1480 infants (96% of in-state VLBW births), and complete data were available for 1413 infants (92% of in-state VLBW births). Table 1 depicts the birth weight distribution of the births and the number of infants for whom data were missing or incomplete. The mean gestational age of the study infants was 28.7 weeks (SD: 2.6), and the median gestational age was 29 weeks (range: 22–37 weeks).

Survival and CLD in 1994

The 1994 survival and pulmonary outcomes by birth weight category are shown in Table 1. In 1994, 78% of the study population survived to 36 weeks' PMA. Survival rates were related inversely to birth weight; 94% of infants with birth weights from 1001 to 1500 g survived compared with 58% of infants with birth weights from 500 to 1000 g ($P < .0001$; RR: 0.64; 95% CI: 0.60–0.68).

Among the survivors in 1994, 25% met our definition of CLD with 4% receiving ventilator support and 21% receiving supplemental oxygen at 36 weeks' PMA. The rate of CLD was related inversely to birth weight. Among infants with birth weights from 500 to 1000 g, the incidence of CLD was 46% compared with 13% for infants with birth weights from 1000 to 1500 g ($P < .0001$; RR: 3.5; 95% CI: 2.8–4.3). Table 1 also presents the outcomes at 30 days of age.

Ventilator therapy for >48 hours remained a significant risk factor for CLD in 1994 and accounted for 89% of infants with CLD at 36 weeks' PMA (Table 2). The effect of ventilator therapy duration was modified by birth weight; the RR of CLD for infants 751 to 1000 g birth weight was 3.3 (95% CI: 1.6–6.7), whereas the RR for CLD in infants 1251 to 1500 g birth weight was 14.8 (5.3–41.7).

Comparison of Outcomes 1984 Versus 1994

In 1994, there were 101 396 total live births in North Carolina compared with 85 986 in 1984, an increase of 18%. The number of VLBW births increased 34% from 1147 in 1984 to 1540 in 1994. The VLBW rate also increased 15%, from 1.3% to 1.5% of all live births. In 1994, the number of infants with birth weights from 500 to 750 g increased twofold and made up 23% of VLBW infants compared with 15% in 1984. A small increase in VLBW multiple births accounted for <1% of VLBW births. The fetal death rate decreased by 10% from 8.8 to 7.9 per 1000 live births.[6]

In 1994, 79% of the VLBW infants survived to discharge or to 6 months of age if still hospitalized (Table 3). Compared with 1984, there was a significant increase in survival across all birth weight categories. The greatest difference occurred in the 500 to 750 g birth weight group with 54% more of these infants surviving in 1994 compared with 1984.

TABLE 1. Distribution and Outcomes of Infants in 1994 With Birth Weights From 500 to 1500 Grams

Birth Weight (g)	In-state Births *n*	No Data *n* (%)	Incomplete Data* *n* (%)	30 Days of Age				36 Weeks' PMA			
				Survival† (%)	Vent‡ (%)	O_2‡ (%)	CLD‡ (%)	Survival† (%)	Vent‡ (%)	O_2‡ (%)	CLD‡ (%)
500–750	346	8 (2)	4 (1)	39	65	27	92	37	12	45	57
751–1000	345	14 (4)	9 (3)	84	34	38	72	84	7	34	41
1001–1250	409	17 (4)	23 (6)	93	6	29	35	92	2	17	19
1251–1500	440	21 (5)	31 (7)	95	2	12	14	95	0.5	7	8
500–1500	1540	60 (4)	67 (4)	79	18	25	44	78	4	21	25

* Survival data known; pulmonary outcome unknown.
† Expressed as percent of live births for whom complete data are available.
‡ Expressed as percent of survivors at each age.

TABLE 2. Comparisons of Outcomes at 36 Weeks' PMA in 1994 by Duration of Ventilator Therapy

Birth Weight (g)	Ventilator >48 Hours		No Ventilator or Ventilator <48 Hours		RR (95% CI)
	Survivors	% CLD	Survivors	% CLD	
500–750	123	57	0		
751–1000	220	46	49	18	3.3 (1.6–6.7)
1001–1250	172	33	169	6	5.5 (2.9–10.4)
1251–1500	106	23	262	2	14.8 (5.3–41.7)
500–1500	621	41	480	5	8.5 (5.5–13.0)

TABLE 3. Survival by Birth Weight Groups

Birth Weight (g)	Births		% In-hospital Survival*		RR (95% CIs)
	1984	1994	1984	1994	
500–750	167	338	24	37	1.56 (1.15–2.11)
751–1000	248	331	65	82	1.27 (1.14–1.41)
1001–1250	300	392	87	93	1.07 (1.01–1.12)
1251–1500	380	419	91	95	1.05 (1.01–1.09)
500–1500	1095	1480	74	79	1.06 (1.02–1.11)

* In-hospital survival, alive at discharge or at 6 months of age if still hospitalized, expressed as the percentage of live births for which survival outcome is known.

TABLE 4. Survival and Pulmonary Outcomes of At-risk* Infants in 1984† and 1994 at Three Postnatal Ages

Birth Weight	30 Days			3 Months			6 Months		
	1984	1994	RR (CI)	1984	1994	RR (CI)	1984	1994	RR (CI)
500–750 g									
No. at risk	46	131							
% Vent	87	64	0.7 (0.6–0.9)	9	4	0.4 (0.1–1.3)	0	1	
% O_2	9	26	3.0 (1.1–8.0)	11	37	3.0 (1.3–6.9)	2	16‡	6.0 (0.8–42.9)
% CLD	96	90	0.94 (0.87–1.02)	20	41	1.8 (0.99–3.3)	2	17‡	6.3 (0.9–44.8)
% Interval deaths				20	6‡	0.3 (0.1–0.8)	4	0‡	0.3 (0.1–0.6)
751–1000 g									
No. at risk	142	222							
% Vent	56	41	0.7 (0.6–0.9)	13	4	0.3 (0.1–0.6)	4	1	0.3 (0.1–1.2)
% O_2	14	41	2.9 (1.9–4.5)	13	23	1.6 (1.01–2.6)	6	9	1.5 (0.7–3.2)
% CLD	70	82	1.2 (1.03–1.3)	27	27	1.0 (0.7–1.4)	10	10	1.0 (0.5–1.8)
% Interval deaths				6	1‡	0.2 (0.1–0.8)	5	2‡	0.2 (0.1–0.6)
1001–1250 g									
No. at risk	146	174							
% Vent	25	11	0.4 (0.3–0.7)	5	1	0.2 (0.1–1.1)	0.7	0.6	0.8 (0.1–12.9)
% O_2	23	41	1.8 (1.3–2.5)	3	14	5.0 (1.8–14.0)	1	4	2.9 (0.6–13.5)
% CLD	48	52	1.1 (0.9–1.3)	9	15	1.7 (0.9–3.1)	2	4	2.1 (0.6–8.0)
% Interval deaths				2	1	0.6 (0.1–3.3)	2	0	0.3 (0.1–1.4)
1251–1500 g									
No. at risk	112	106							
% Vent	16	7	0.4 (0.2–0.9)	3	1	0.3 (0.04–3.2)	1	0	—
% O_2	9	34	3.8 (2.0–7.3)	3	11	3.7 (1.1–13.0)	2	4	2.0 (0.4–10.9)
% CLD	25	40	1.6 (1.1–2.4)	5	12	2.0 (0.8–5.2)	3	4	1.4 (0.3–5.9)
Death*				4	0		0	0	
Total									
No. at risk	446	633							
% Vent	39	31	0.82 (0.70–0.96)	8	3	0.3 (0.2–0.6)	2	1	0.5 (0.2–1.5)
% O_2	15	37	2.4 (1.9–3.1)	7	21	2.9 (2.0–4.3)	3	8	2.6 (1.5–4.8)
% CLD	54	68	1.3 (1.2–1.4)	15	24	1.5 (1.2–2.0)	5	9‡	2.3 (1.4–3.8)
% Interval deaths				6	2‡	0.3 (0.2–0.7)	3	0.5‡	0.3 (0.2–0.5)

* Survived 30 days and ventilated >48 hours.
† Data from Kraybill et al, 1987.
‡ $P < .05$ compared with 1984.

The 1994 pulmonary outcomes with comparisons to 1984 are shown in Table 4. In 1994, 633 VLBW infants (43%) were at risk compared with 41% of VLBW infants in 1984. In 1994, among at-risk infants, 68% had CLD at 30 days of age, compared with 54% in 1984 (RR: 1.27; 95% CI: 1.15–1.40). Significant increases in 1994 CLD rates among at-risk infants also were observed at 3 and 6 months. This increase in CLD was coincident with decreased postneonatal mortality at 3 and 6 months in 1994, compared with 1984 within all birth weight groups except for infants with birth weights of 1001 to 1250 g. For all infants and within each birth weight category, significantly fewer infants in 1994 were receiving ventilator therapy at 30 days of age compared with 1984. Conversely, the rates of supplemental oxygen therapy at 30 days and 3 months increased significantly for each birth weight category, as well as for all infants.

DISCUSSION

From 1984 to 1994, the rate of VLBW births in North Carolina rose at nearly twice the rate of rise of the overall birth rate. The increase was highest among infants with birth weights from 500 to 750 g. In part, this increase may reflect reporting differences. Although the definition of a live birth has remained constant over this period,[6] in 1994 extremely small infants might have been reported more often as live births. It is probable that in 1984 some live-born infants of extremely low birth weight were judged to be nonviable and considered fetal deaths. Moreover, the fetal death rate decreased by 10% from 1984 to 1994. More aggressive perinatal care of fetuses at the margin of viability also may have caused the noted reduction in fetal mortality. The relative increase in the rate of VLBW births may be a response to changing prenatal conditions resulting in preterm delivery. As the use of techniques to augment fertility has increased, the rate of multiple births has risen. However, this increase is seen primarily in the 1501 to 2500 g birth weight group.[7] In addition, it is possible that the population has changed to become one with an increased risk for preterm labor. Finally, the increase in VLBW births may reflect not only an increase in the number of preterm infants but also an increase in the proportion of infants with intrauterine growth restriction.

In 1994, among VLBW infants in North Carolina, the incidence of CLD, defined as treatment with either supplemental oxygen or ventilation, was 44% at 30 days' postnatal age and 25% at 36 weeks' PMA. Both of these rates suggest that CLD continues to be a common morbidity among preterm infants. However, the latter definition may have greater significance. Oxygen supplementation at early postnatal ages may be required because of lung immaturity rather than a pathologic process.[8] Observations at later time points may have greater prognostic value. Shennan et al[9] found that a supplemental oxygen requirement at 36 weeks' PMA had nearly twice the predictive value for abnormal pulmonary outcomes during infancy compared with oxygen dependency at 28 days of age. This was supported by deRegnier et al,[10] who found that an increased risk of neurodevelopmental, sensory, and growth impairments, in addition to an increased rate of hospital readmission had a higher association with oxygen dependency at 36 weeks' PMA, compared with oxygen dependency at 28 days' postnatal age. Palta et al[11] reported recently that oxygen therapy at 36 weeks' PMA had both strong positive and negative predictive values for hospital readmission, asthma, and use of pulmonary medications, although radiographic evidence of CLD at 30 days provided the best predictive value. Thus, supplemental oxygen dependency at 36 weeks' PMA serves as an improved predictive measure of outcome for the VLBW infant.

Our study also confirmed that ventilator therapy for >48 hours identifies an at-risk group of infants for development of CLD. It is possible that this group is characterized by a poor response to exogenous surfactant therapy[12] or that any use of mechanical ventilator therapy leads to CLD.[13,14]

We confirmed the strong inverse relationship among birth weight and both mortality and CLD. Of infants with birth weight 500 to 1000 g, 48% developed CLD compared with 12% of infants with birth weight from 1001 to 1500 g. The data emphasize the fact that CLD continues to be a significant public health concern that is linked to the improved survival of extremely premature infants.

The 1994 North Carolina CLD rate at 36 weeks' PMA is similar to the rate reported recently by the large multicenter Neonatal Research Network in the United States (25% vs 19%).[4] However, North Carolina had significantly higher rates of CLD compared with a contemporary population-based study from outside the United States. Fenton et al[15] investigated the incidence of CLD in two regions in Canada and England in 1990. Although rate of survival was similar with that for our cohort, the 36-week CLD rates were 6% and 18% in these two regions compared with 25% in North Carolina. The differences between these populations may only reflect differences in demography and medical care systems. However, examination of these latter differences may provide an avenue for investigation of antecedents of CLD.

The incidence of CLD among high-risk infants was greater in our study population compared with the incidence in a similar cohort in 1984. This increase was coincident with increased survival resulting from decreases in both neonatal mortality and postneonatal mortality before hospital discharge. It is possible that the increased incidence of CLD is directly attributable to the survival of sicker infants at greater risk for CLD. This hypothesis is supported by studies that have suggested that the greatest impact of surfactant therapy is improved survival rather than reduction in CLD.[16,17] Other studies have also noted increases in survival and CLD concurrently with increased use of both antenatal steroids and surfactant therapy.[3,18]

Despite an increase in the percentage of infants with CLD in 1994 compared with 1984, there was a notable shift in their respiratory support requirements. At all measured time points, we found a greater proportion of the infants with CLD receiving supplemental oxygen alone and fewer infants on the ventilator. This shift from ventilator to oxygen therapy was observed in all birth weight groups. At 30 days of age, 87% of infants with birth weights between 500 and 750 g were receiving ventilator therapy in 1984 compared with 69% in 1994. For the total group of at-risk infants, 39% remained on the ventilator at 30 days in 1984 compared with 32% in 1994. The explanation for this shift in the method of respiratory support is beyond the scope of this study. However, this benefit is reasonably attributable to changes in respiratory care, including surfactant therapy, postnatal steroids, and possibly differences in techniques of mechanical ventilation.

It is possible that the increasing incidence of CLD reflects a change in the criteria for oxygen therapy. In 1994, determination of the requirement for oxygen was based primarily on measurements of oxygen saturation by pulse oximetry; this technology was not used routinely in 1984. It seems likely that at least a portion of the additional infants receiving oxygen in 1994 compared with 1984 were treated because of this advancement in the monitoring of blood oxygenation.

There were limitations in our study design. First, we did not exclude infants with congenital anomalies in whom survival or CLD may have been influenced by more complex factors such as pulmonary hypoplasia. Infants with intrauterine growth restriction were not identified. Therefore, we cannot determine whether there was a change in the proportion of either group of infants in the study populations between 1984 and 1994. Kayata et al[19] reported that among infants with birth weights $<$1500 g, the incidence of CLD was lower in growth restricted infants. In addition, our method of data collection did not account for infants who were discharged from the nursery without supplemental oxygen and who later developed a need for a such support, although this would be expected to occur rarely. Finally, the sample is missing 60 infants. Although study data were not collected on these infants, information from the State Center for Health Statistics indicated a relatively even birth weight, geographic, and institutional distribution.

CONCLUSION

In summary, CLD as a complication of prematurity remains a significant morbidity and public health problem. Increased survival of VLBW infants magnifies the importance of this problem. As the proportion of VLBW infants has grown, the impact of CLD has increased. Our data suggest that recent changes in neonatal care have reduced the severity of CLD, evidenced by a shift from mechanical ventilation to oxygen therapy. Current innovative therapies under investigation, eg, antioxidants, may reduce the severity further. However, future studies should also focus on identifying the potentially alterable antecedents of CLD so that medical and social interventions can be developed to prevent the disease.

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