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Longitudinal Growth of Hospitalized Very Low Birth Weight Infants

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ABSTRACT. *Background.* The interpretation of growth rates for very low birth weight infants is obscured by limited data, recent changes in perinatal care, and the uncertain effects of multiple therapies.

Objectives. To develop contemporary postnatal growth curves for very low birth weight preterm infants and to relate growth velocity to birth weight, nutritional practices, fetal growth status (small- or appropriate-for-gestational-age), and major neonatal morbidities (chronic lung disease, nosocomial infection or late-onset infection, severe intraventricular hemorrhage, and necrotizing enterocolitis).

Design. Large, multicenter, prospective cohort study.

Methods. Growth was prospectively assessed for 1660 infants with birth weights between 501 to 1500 g admitted by 24 hours of age to 1 of the 12 National Institute of Child Health and Human Development Neonatal Research Network centers between August 31, 1994 and August 9, 1995. Infants were included if they survived >7 days (168 hours) and were free of major congenital anomalies. Anthropometric measures (body weight, length, head circumference, and midarm circumference) were performed from birth until discharge, transfer, death, age 120 days, or a body weight of 2000 g. To obtain representative data, nutritional practices were not altered by the study protocol.

Results. Postnatal growth curves suitable for clinical and research use were constructed for body weight, length, head circumference, and midarm circumference. Once birth weight was regained, weight gain (14.4–16.1 g/kg/d) approximated intrauterine rates. However, at hospital discharge, most infants born between 24 and 29 weeks of gestation had not achieved the median birth weight of the reference fetus at the same postmenstrual age. Gestational age, race, and gender had no effect on

growth within 100-g birth weight strata. Appropriate-for-gestational age infants who survived to hospital discharge without developing chronic lung disease, severe intraventricular hemorrhage, necrotizing enterocolitis, or late onset-sepsis gained weight faster than comparable infants with those morbidities. More rapid weight gain was also associated with a shorter duration of parenteral nutrition providing at least 75% of the total daily fluid volume, an earlier age at the initiation of enteral feedings, and an earlier age at achievement of full enteral feedings.

Conclusions. These growth curves may be used to better understand postnatal growth, to help identify infants developing illnesses affecting growth, and to aid in the design of future research. They should not be taken as optimal. Randomized clinical trials should be performed to evaluate whether different nutritional management practices will permit birth weight to be regained earlier and result in more rapid growth, more appropriate body composition, and improved short- and long-term outcomes. *Pediatrics* 1999;104:280–289; *very low birth weight infant, growth curves, National Institute of Child Health and Human Development Neonatal Research Network.*

ABBREVIATIONS. VLBW, very low birth weight; PN, parenteral nutrition; SGA, small-for-gestational age; AGA, appropriate-for-gestational age; CLD, chronic lung disease; NEC, necrotizing enterocolitis; NICHD, National Institute of Child Health and Human Development; HC, head circumference; MAC, midarm circumference.

Daily evaluation of body weight is a standard practice in the care of very low birth weight (VLBW) preterm infants, and changes in weight are used to adjust fluid and nutritional management and to help identify infants with signs of illness. However, such management is often based on practice style rather than an understanding of the expected weight gain for infants who have different birth weights, gestational ages, postnatal ages, and clinical problems. Weight changes during the first week of life primarily reflect fluctuation of total body water, whereas changes beyond the second week of life seem to reflect growth in response to nutritional support.¹

In 1948, Dancis et al² published growth curves derived from 100 preterm infants with birth weights ranging from 1000 to 2500 g; a curve for infants weighing 750 g at birth that was based on the observations for only a few survivors was also included. Those curves are still widely used today, despite

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major changes in many aspects of neonatal care, including nutritional support. However, "no attempt was made to achieve statistical accuracy in constructing these curves" and the curves "represent what the premature infant who develops without complications will do when fed and handled in a certain arbitrary manner."² Dancis and his colleagues² also stated that the "chief variable in determining the weight curve of such a premature infant is the feeding policy."

More recent reports³⁻⁸ have described postnatal weight changes in surviving preterm infants. The growth rates for VLBW infants exceeded those predicted by the Dancis curves.² The authors suggested that the differences may reflect changes in nutritional management and cautioned that the observed growth rates may not be optimal. Although a greater number of extremely low birth weight infants were included in these studies, data for infants with birth weights <750 g are still limited.

We have performed a multicenter, prospective cohort study to define postnatal longitudinal growth for VLBW infants. Our specific objectives were: 1) to develop postnatal growth curves for VLBW preterm infants that would permit an assessment of growth velocity; 2) to relate growth velocity and nutritional practices (duration of parenteral nutrition [PN], age at first enteral feeding and age at full enteral feeding); 3) to compare growth velocity in infants who are small-for-gestational age (SGA) with infants who are appropriate-for-gestational age (AGA); and 4) to relate growth velocity to several common, major morbidities, including chronic lung disease (CLD), nosocomial infection (or late-onset infection) and necrotizing enterocolitis (NEC). These growth data may be useful in identifying preterm infants who are growing slowly despite current nutritional support and in designing and performing clinical trials of nutritional interventions.

PATIENTS AND METHODS OF DATA COLLECTION

Data were collected on 1660 infants with birth weights between 501 to 1500 g who were inborn or admitted at 24 hours of age or less to 1 of the 12 National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers between August 31, 1994 and August 9, 1995, survived >7 days (168 hours) and were free of major congenital anomalies. Five hundred twelve additional infants admitted to NICHD Neonatal Research Network centers were excluded during the study period; 220 did not survive longer than 1 week, 133 were ineligible because they were admitted after 24 hours of age, had major congenital anomalies or a birth weight <501 g, and 160 for various other reasons, but primarily because study-specific data forms were not submitted. Growth measures were performed from birth until a body weight of 2000 g was reached ($n = 898$), until discharge ($n = 482$), transfer ($n = 173$), death ($n = 84$), or age 120 days ($n = 23$). To obtain representative data, nutritional practices and other aspects of neonatal care were not altered by the study protocol. The participating centers included: the University of Tennessee at Memphis (study population [n] = 233), the University of Miami ($n = 171$), the Rainbow Babies and Children's Hospital at Case Western Reserve University ($n = 165$), the Wayne State University School of Medicine ($n = 165$), the University of Texas Southwestern Medical Center at Dallas ($n = 163$), the Indiana University ($n = 147$), the Women and Infants Hospital at Brown University ($n = 147$), the Grady Memorial Hospital at Emory University ($n = 124$), the Yale-New Haven Children's Hospital at Yale University ($n = 100$), the Stanford University ($n = 96$), the University of Cincinnati ($n = 84$), and the University of New Mexico ($n = 65$).

Data for each eligible infant were prospectively collected using

previously described definitions for data variables and clinical conditions.⁹⁻¹¹ Gestational age in completed weeks was based on best obstetrical estimate, if one existed, otherwise it was estimated from the last menstrual period, standard obstetrical observations, and ultrasonography.¹¹ Trained research nurses performed the anthropometric measurements and abstracted study data from the infants' charts. The research nurse from each participating center who was primarily responsible for performing the anthropometric measurements attended a training session before the start of the study; the measurement techniques were standardized at that training session. Morbidity and mortality data were analyzed for all infants until discharge, transfer, death, or 120 days after birth, whichever came first. SGA was defined as birth weight less than the 10th percentile for gender according to Arbuckle et al.¹² CLD was defined by the administration of oxygen at 36 weeks of postmenstrual age. Late-onset sepsis was defined as a positive blood or cerebral spinal fluid culture obtained in the presence of compatible clinical signs of septicemia occurring after 72 hours of age or culture negative clinical infection after 72 hours of age for which the infant received antibiotics for 5 or more days. Infants were considered to have definite NEC if they met or exceeded the modified Bell's staging criteria IIA.¹³ Severe intraventricular hemorrhage was defined as a grade 3 or 4 hemorrhage according to the grading scale described by Papile et al.¹⁴ The information was entered onto a local personal computer using a distributed data entry system developed by the George Washington University Biostatistics Coordinating Center. Data were electronically transferred weekly to the coordinating center for editing, including checks for discrepancies and inconsistencies. Edit reports were sent to each center for clarification or corrections.

Anthropometric Measurements

Body weight was recorded daily for a minimum of 14 days or until birth weight was regained, whichever occurred later, and then weekly. Measurements were performed at a standard time each day with digital electronic scales (reading to at least the nearest 10 g). Before the start of the study and at 4 to 6 month intervals, the accuracy of the scales were verified using standard weights.

Recumbent length was measured weekly with a Premie Length Board (O'Leary, Ellard Instrumentation LTD, Seattle, WA). One examiner held the infant's head in a vertical position with the top of the head touching the fixed headboard, while a second examiner extended the legs and firmly placed the movable footboard against the infant's heels.¹⁵

Head circumference (HC) was measured weekly. It was determined by applying a paper measurement tape firmly around the head above the supraorbital ridges, at the most prominent part of the frontal bulge anteriorly, and over the part of the occiput that gave the maximum circumference.¹⁶

Midarm circumference (MAC) was measured weekly. It was determined by applying a paper measurement tape firmly around the upper arm at the midpoint; the midpoint was located by measuring the distance between the acromion and the olecranon with the arm in a horizontal position.¹⁶ If possible, the same arm was used throughout the infant's hospitalization.

Length, HC, and MAC measurements were each performed twice. An average of the two values was recorded. If the measurements differed by more than 5%, additional measurements were performed and the median value was recorded.

Statistical Methods

The infants were divided in 100-g birth weight intervals from 501 g to 1500 g, and separate curves were constructed for weight, length, HC, and MAC within each interval. To accommodate patient-to-patient variation, mixed-effects models were used.¹⁷ Because the measurements (weight in particular) vary nonlinearly with time, quadratic regression splines^{18,19} were used for the systematic part of the models. These models have the ability to fit arbitrary smooth nonlinear functions while using a small number of parameters. The model for body weight (W) on day of life t , expressed as a piecewise quadratic curve is:

$$W_t = \begin{cases} BW + \beta_1 t + \beta_2 (T_1 - t)^2 + \beta_3 (T_2 - t)^2 + \epsilon_i & \text{for } t \leq T_1 \\ BW + \beta_1 t + \beta_3 (T_2 - t)^2 + \epsilon_i & \text{for } T_1 < t \leq T_2 \\ BW + \beta_1 t + \epsilon_i & \text{for } t > T_2 \end{cases}$$

The model assumes that body weight (W_t) decreases from birth weight (BW) before age T_1 reaches its minimum in the time inter-

val between T_1 and T_2 , and then increases linearly beyond T_2 . The error terms, ϵ_i , are assumed to be independent and identically distributed with a normal distribution. The parameters, β_1 , β_2 , and β_3 , are patient specific random effects and are estimated by maximum likelihood, conditionally on the knot positions, T_1 and T_2 . The fit is repeated with a grid search for T_1 and T_2 until convergence. Similar models were used to construct curves for length, HC, and MAC.

A reference population of infants who were AGA and survived to discharge without developing severe intraventricular hemorrhage, NEC, CLD, or late-onset sepsis was identified. This population was stratified by 200-g birth weight intervals to increase the number of reference infants within each birth weight interval below 1101 g. Curves comparing growth between infants in this reference population and the remaining infants with those morbidities were constructed, as described above, with the infants within each of the 200-g birth weight intervals from 501 to 1500 g. Additional curves prepared within these 200-g birth weight intervals compared growth between: 1) AGA and SGA infants; 2) infants with and without CLD; 3) infants who had and who had not experienced late-onset sepsis; 4) infants who received at least 75% of their total daily fluid volume as PN for the median duration or less and infants who received that amount of PN for longer than the median duration; 5) infants who were started on enteral nutrition at the median age or earlier and infants who were started at greater than the median age; and 6) infants who achieved full enteral nutrition (>100 kcal/kg/d) at the median age or earlier and infants who were older than the median age.

The average daily increments for body weight (g/d and g/kg/d) and the average weekly increments for length, HC, and MAC were computed for the period between the time that the infant regained birth weight and discharge, transfer, death, age 120 days, or until a body weight of 2000 g was reached. Seventeen infants who never regained birth weight were excluded from these calculations.

The velocity of growth for an individual infant was characterized by the average daily weight gain after birth weight was regained, and by the weekly average gains in length, HC, and MAC. Pearson correlations were obtained among these four measures, and between the measures of gestational age, race (black versus not black), and gender. In addition, Pearson correlations were obtained between the age at first enteral feeding and the age at which full enteral feedings were achieved.

RESULTS

Characteristics of the entire study population stratified by 100-g birth weight intervals are displayed in Tables 1 and 2. Each 100-g birth weight interval between 501 and 1500 g, except for the 501 to 600 g strata, contained more than 100 infants who survived for >7 days (168 hours). Although the percentages of

males, whites, SGA infants, and infants who experienced morbidities are similar to those previously reported by the NICHD Neonatal Research Network,⁹⁻¹¹ males and whites are underrepresented and SGA infants are overrepresented in study infants with birth weights <701 g. As expected, the number of days that PN provided at least 75% of the total daily fluid volume, the age in days when enteral feedings were initiated and the age in days when full enteral feedings were achieved tended to decrease progressively as birth weight increased.

Growth velocity by 100-g birth weight intervals is listed in Table 3. All available anthropometric measurements were used from all infants, regardless of their nutritional status or clinical course. Statistically significant, positive correlations between the velocities of weight, length, HC, and MAC gains were demonstrated, indicating that infants who tended to grow fast in one measure tended to grow fast in the others. Within each 100-g birth weight interval, gestational age, race, and gender had no effect on the growth rate. Average daily weight gain (g/kg body weight/d) after regaining birth weight was similar across 100-g birth weight intervals, ranging between 14.4 and 16.1 g/kg/d (1.44%/d to 1.61%/d). Similarly, weekly growth in length, HC, and MAC was similar across 100-g birth weight intervals, averaging ~0.9 cm/wk, 0.9 cm/wk, and 0.35 cm/wk, respectively.

Curves plotting body weight, length, HC, and MAC versus postnatal age for each 100-g birth weight stratum in this population are shown in Figs 1, 2, 3, and 4, respectively. Similar to the data used for Table 3, Figs 1 to 4 are based on anthropometric measurements from all infants, regardless of their nutritional status or clinical course.

The characteristics of the reference population are shown in Table 4. Growth curves constructed from models which estimated growth within each 200-g birth weight interval for the reference population and for the remaining infants with morbidities are shown in Fig 5. The curves for both groups of infants with birth weights 501 to 700 g are similar for the first

TABLE 1. Infant Characteristics

	Birth Weight Interval (g)									
	501-600	601-700	701-800	801-900	901-1000	1001-1100	1101-1200	1201-1300	1301-1400	1401-1500
Number	61	136	163	144	191	168	175	198	211	213
Gestational age (wk)*	24.8 ± 1.9	25.2 ± 1.8	25.7 ± 1.5	26.8 ± 2.0	27.6 ± 1.9	28.5 ± 2.0	29.0 ± 2.1	29.8 ± 1.9	30.4 ± 1.9	30.9 ± 1.9
% Male	36.1	44.1	56.4	52.1	53.9	49.4	46.0	48.0	55.5	49.3
% White	26.2	33.8	36.8	37.5	35.6	38.1	35.4	31.8	34.6	46.0
% SGA†	52.5	42.2	27.3	18.6	18.5	21.0	22.8	19.9	19.0	15.2
% Survival‡	63.9	84.6	84.0	93.1	91.6	98.8	98.9	99.0	100.0	100.0
% Chronic lung disease§	52.4	37.9	43.3	28.7	25.5	18.1	13.2	10.2	6.3	8.5
% Late-onset sepsis	80.3	77.9	71.8	64.6	51.3	45.2	30.9	25.3	17.1	17.5
% Severe IVH¶	24.6	20.6	19.0	14.0	12.0	7.2	5.2	5.1	2.0	1.6
% NEC#	8.2	15.4	12.3	10.4	8.9	7.1	4.0	4.0	1.9	3.3

Abbreviations: SGA, small-for-gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

* Best obstetrical estimate (mean ± SD).

† Birth weight <10 percentile according to Arbuckle et al.¹²

‡ Survival of infants meeting inclusion criteria (ie, survival >168 hours).

§ Oxygen dependence at 36 weeks postmenstrual age.

|| Sepsis occurring after 72 hours of age with proven culture and/or treated with antibiotics for >5 days.

¶ Grade 3-4 IVH.¹⁴

NEC, Bell's Stage II or worse.¹³

TABLE 2. Nutritional Characteristics

Birth Weight Interval (g)	Duration PN $\geq 75\%$ * (Days)	Age at First Enteral Feeding (Days)	Age at Full Enteral Feeding (Days)	Age to Regain Birth Weight† (Days)
501–600	20.8 \pm 15.8‡	9.2 \pm 5.5	33.8 \pm 15.6	15.2 \pm 12.2
601–700	20.7 \pm 15.0	9.5 \pm 9.5	34.0 \pm 19.3	16.7 \pm 12.6
701–800	15.6 \pm 11.3	8.0 \pm 6.6	27.3 \pm 15.2	17.2 \pm 12.3
801–900	14.0 \pm 11.2	6.2 \pm 5.6	23.0 \pm 13.8	15.5 \pm 10.1
901–1000	12.2 \pm 9.9	5.7 \pm 5.1	20.8 \pm 12.5	14.4 \pm 9.7
1001–1100	10.3 \pm 9.2	4.8 \pm 3.6	18.3 \pm 12.1	12.8 \pm 7.5
1101–1200	7.4 \pm 6.8	3.9 \pm 3.7	14.2 \pm 9.5	13.2 \pm 8.5
1201–1300	5.7 \pm 5.0	3.1 \pm 2.6	12.1 \pm 8.0	11.5 \pm 7.6
1301–1400	4.8 \pm 5.6	2.9 \pm 2.9	10.7 \pm 7.6	12.0 \pm 7.3
1401–1500	4.9 \pm 5.2	2.8 \pm 2.7	10.7 \pm 7.7	11.6 \pm 6.6

Abbreviation: PN, parenteral nutrition.

* Duration of PN providing at least 75% of the total daily fluid volume.

† Birth weight regained and maintained for 2 days.

‡ Mean \pm SD.

TABLE 3. Growth Velocity by Birth Weight Interval*

Birth Weight Interval, g (n)	Weight Gain		Length (cm/wk)	Head Circumference (cm/wk)	Midarm Circumference (cm/wk)
	(g/d)	(g/kg/d)			
501–600 (53)	15.27	13.99	0.99	0.90	0.42
601–700 (128)	16.81	13.46	0.95	0.89	0.39
701–800 (155)	18.60	13.96	1.01	0.94	0.42
801–900 (139)	20.06	14.46	1.02	0.94	0.42
901–1000 (184)	21.04	14.63	1.02	0.97	0.42
1001–1100 (163)	22.83	15.22	1.00	0.94	0.42
1101–1200 (171)	24.73	15.98	1.00	0.95	0.43
1201–1300 (187)	26.34	16.28	0.99	1.00	0.48
1301–1400 (200)	27.15	16.17	0.96	0.89	0.45
1401–1500 (203)	27.77	16.00	0.86	0.74	0.25

* The average daily increments for body weights (g/d and g/kg/d) and the average weekly increment for length, head circumference, and midarm circumference were computed for the period between the time that birth weight was regained and discharge, transfer, death, age 120 days, or until a body weight of 2000 g was reached.

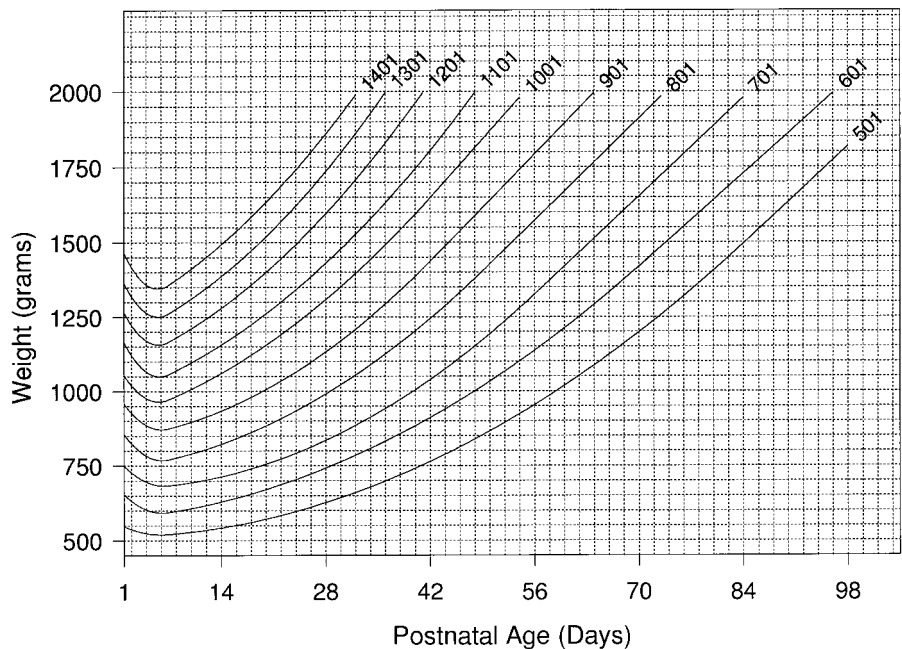


Fig 1. Average daily body weight versus postnatal age in days for infants stratified by 100-g birth weight intervals.

42 days; afterward the curves separate with a difference of ~ 175 g present at 84 days of age. However, because only 4% of the infants with birth weights 501 to 700 g were included in the reference population, the validity of that curve is questionable. A comparison of the curves for infants with birth weights >700

g demonstrated that infants in the reference population tended to regain birth weight sooner, weighed 20 to 40 g more at 28 days of age, and weighed at least 100 g more at 56 days of age than infants of comparable birth weight with morbidities.

The growth of infants with and without CLD and

Fig 2. Average weekly length versus postnatal age in weeks for infants stratified by 100-g birth weight intervals.

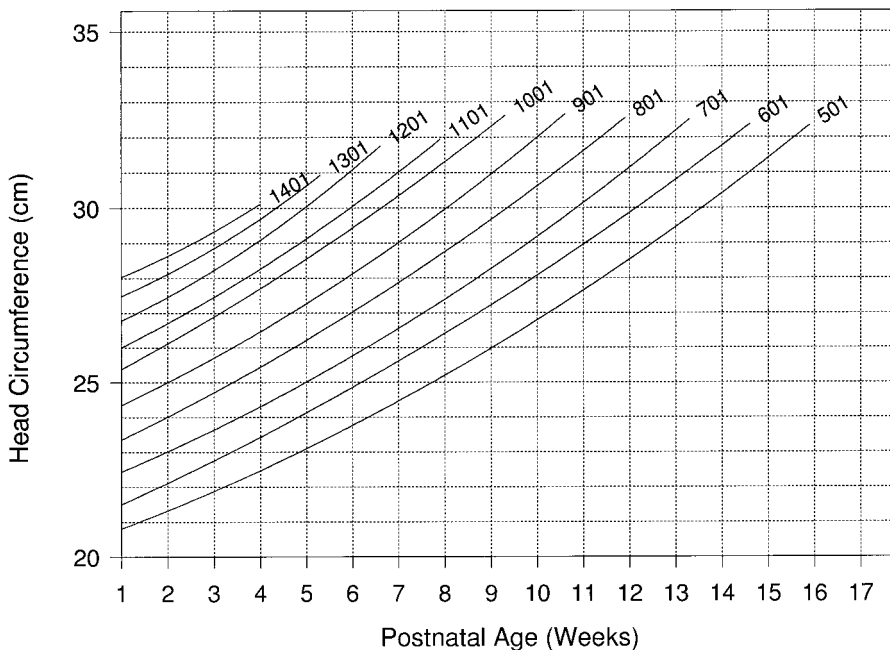
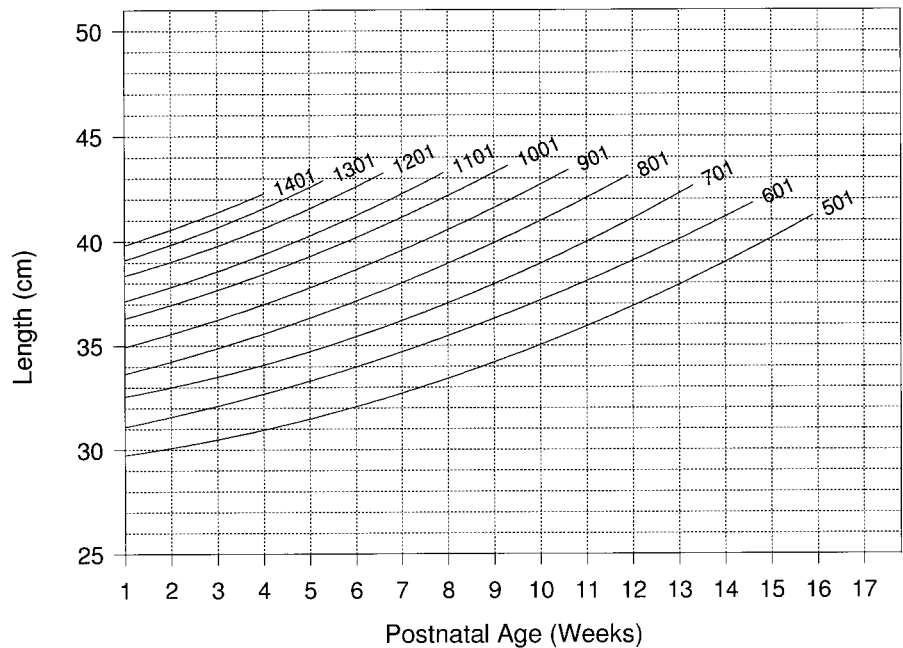


Fig 3. Average weekly head circumference versus postnatal age in weeks for infants stratified by 100-g birth weight intervals.

of infants who experienced and who did not experience late-onset sepsis was also compared. These analyses revealed curves similar to those comparing the reference population to the infants with morbidities in Fig 5. Although the growth curves of infants with birth weights 501 to 700 g were not affected by the development of CLD, the curves for the other infants with CLD and the curves for the infants with late-onset sepsis were slower than those for infants without CLD or late-onset sepsis; specifically, a body weight of 2000 g was reached ~1 to 2 weeks later than the comparable birth weight cohort without those morbidities. During the study period ~22% of the infants with birth weights 501 to 1500 g (center range, 10%–34%) received corticosteroids for treat-

ment of CLD; such treatment has been associated with slower growth.^{20,21}

A comparison of the growth of SGA and AGA infants is shown in Fig 6. Within each 200-g birth weight interval the SGA infants returned to birth weight 3 to 5 days sooner, gained weight faster, and reached a body weight of 2000 g ~3 to 7 days earlier than did their comparable AGA birth weight cohort.

Comparisons of the growth curves of infants within 200-g birth weight intervals revealed that infants who received at least 75% of their total daily fluid volume as PN for a shorter time period (median duration or less) gained weight faster; that infants who were started on enteral nutrition earlier (median age or younger) gained weight faster; and that in-

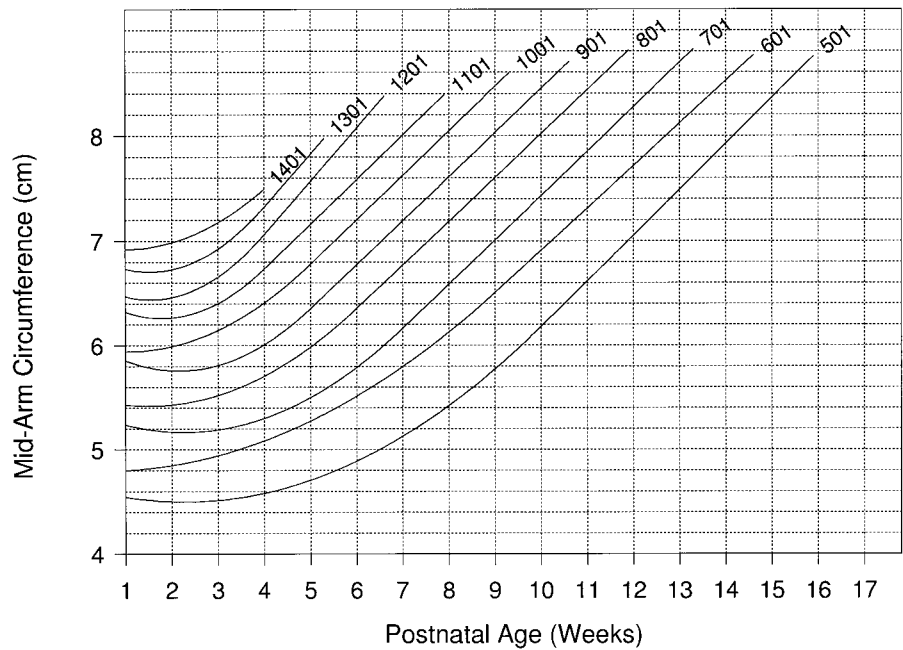


Fig 4. Average weekly midarm circumference versus postnatal age in weeks for infants stratified by 100-g birth weight intervals.

TABLE 4. Reference Population Characteristics

	Birth Weight Interval				
	501–700 g (n = 197)	701–900 g (n = 307)	901–1100 g (n = 359)	1101–1300 g (n = 373)	1301–1500 g (n = 424)
Reference population*	8 (4.1)	32 (10.4)	80 (22.8)	139 (37.3)	219 (51.7)
Gestational age, wk	24.3 ± 1.0†	26.4 ± 2.0	27.7 ± 1.2	29.1 ± 1.6	30.3 ± 1.6
Male, n (%)	2 (25.0)	18 (56.3)	27 (33.8)	58 (41.7)	94 (42.9)
White, n (%)	5 (62.5)	7 (21.9)	24 (30.0)	39 (28.1)	85 (38.8)
Duration (d) PN ≥75%	12.5 ± 7.0	9.1 ± 5.6	6.9 ± 5.3	4.4 ± 3.7	3.7 ± 3.7
Age (d) at first enteral feed	6.0 ± 3.0	5.5 ± 4.2	3.8 ± 2.3	2.8 ± 2.1	2.5 ± 1.8
Age (d) at full enteral feed	24.9 ± 10.4	18.1 ± 7.2	13.6 ± 6.4	10.2 ± 5.6	9.0 ± 4.7
Age (d) to regain birth weight‡	18.6 ± 3.6	17.5 ± 9.6	13.5 ± 6.9	12.5 ± 6.7	12.0 ± 5.9

Abbreviations: PN, parenteral nutrition.

* The reference population [n (%)] was defined as infants who were appropriate-for-gestational age and survived to discharge without developing chronic lung disease, severe intraventricular hemorrhage, necrotizing enterocolitis, or late-onset sepsis.

† Mean ± SD.

‡ Birth weight regained and maintained for 2 days.

infants who achieved full enteral nutrition sooner (median age or younger) gained weight faster. Similar sets of growth curves were obtained with each comparison. However, within each 200-g birth weight cohort, no correlation was found between the age at the first enteral feeding and the age at which full enteral feedings was achieved.

To further examine differences between normal intrauterine growth and our observed rates of postnatal growth, growth curves for study infants with gestational ages 24 to 25 weeks ($n = 218$), 26 to 27 weeks ($n = 364$), and 28 to 29 weeks ($n = 474$) were compared with reference intrauterine growth curves (Fig 7) that were plotted using the smoothed 10th and 50th percentile birth weight-gestational age data recently reported by Alexander et al.²² Although growth data were collected on infants with birth weights up to 1500 g, curves for infants with a gestational age of 30 weeks or more ($n = 547$) were not included because a high percentage of them weigh >1500 g at birth, making such curves from our data unrepresentative. As displayed in Fig 7, each post-

natal growth curve is shifted to the right of the reference intrauterine growth curves. Furthermore, although the birth weights of the study infants are similar to the birth weights of the infants shown on the reference intrauterine growth curve, most of the infants born between 24 to 29 weeks gestation would not have achieved the median birth weight of the reference fetus of the same postmenstrual age, and many would be less than the 10th percentile at hospital discharge.

DISCUSSION

The clinical interpretation of the growth rate for individual VLBW infants is hindered by the multiple factors which may influence growth, the limited number of VLBW infants assessed in previous studies, and the marked changes in perinatal medicine during the past 5 to 10 years. These changes include the widespread use of surfactant replacement therapy, antenatal steroids for pulmonary maturation and central nervous system protection, postnatal steroids for CLD, and percutaneously-inserted central

Fig 5. Growth curves of infants with major morbidities (dashed line) and of reference infants without major morbidities (solid line) plotted by postnatal age in days. The infants are stratified by 200-g birth weight intervals. Reference infants without major morbidities were appropriate-for-gestational age and survived to discharge without developing chronic lung disease, severe intraventricular hemorrhage, necrotizing enterocolitis, or late-onset sepsis.

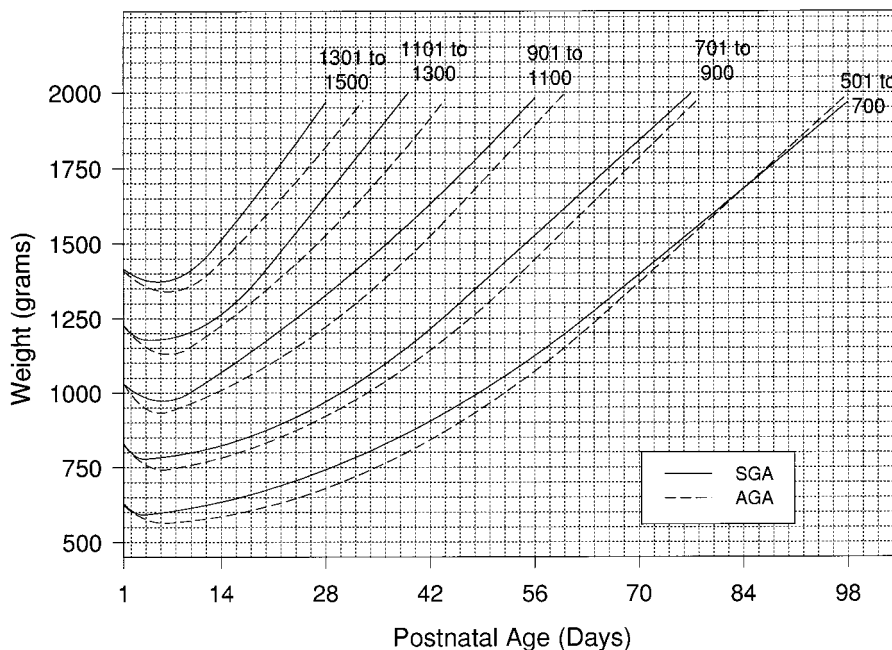
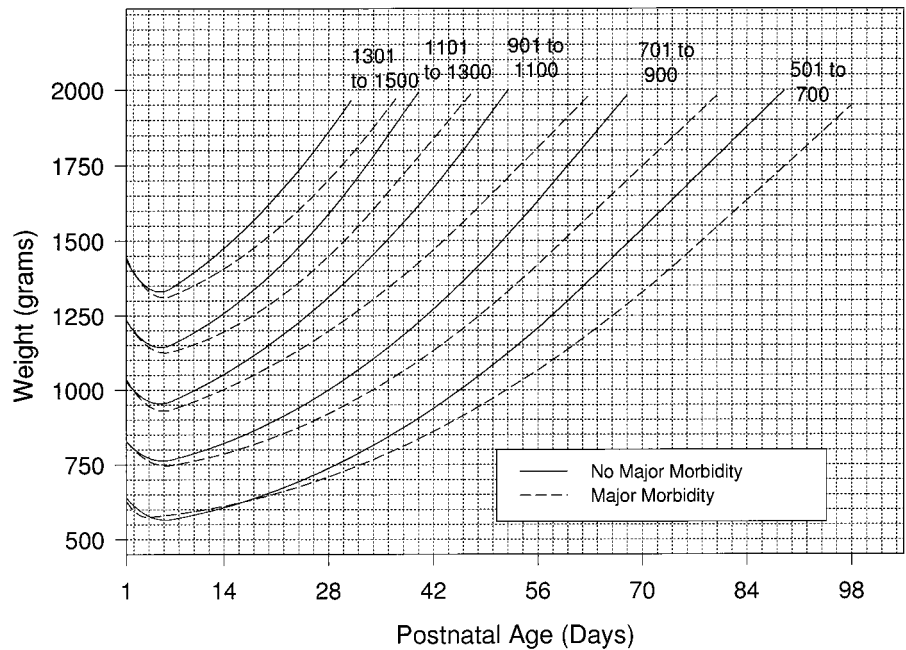


Fig 6. Growth curves of small-for-gestational age infants (solid line) and of appropriate-for-gestational age infants (dashed line) plotted by postnatal age in days. The infants are stratified by 200-g birth weight intervals.

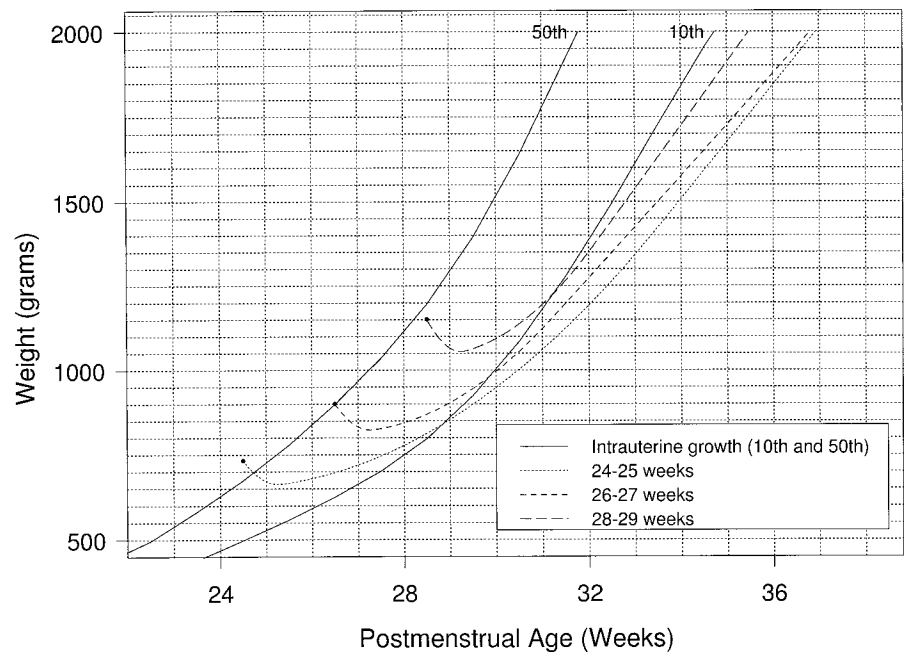
venous catheters for parenteral nutritional support. We therefore chose to prospectively evaluate a large heterogeneous population of VLBW infants in an effort to determine postnatal growth in response to current nutritional practices and as a first step in designing clinical trials in neonatal nutrition aimed at improving postnatal growth and nutritional status.

The goal of nutritional management of VLBW infants that has been favored by the American Academy of Pediatrics Committee on Nutrition^{23,24} is the achievement of postnatal growth at a rate approximating that of the third trimester of intrauterine life. Although the birth weights of infants who deliver prematurely may differ from the weights of undelivered fetuses of the same gestational age, reference

intrauterine growth rates have usually been derived from the 50th percentile curve displayed in published reports of intrauterine growth.^{12,22,25-27} As in our study, gestational age in these reports was usually expressed in completed weeks based on the interval between the date of the last normal menses and the date of live birth.

Since the report by Dancis et al² in 1948, a number of growth curves³⁻⁸ have been published. Depending on the characteristics of the population studied, infants were usually found to regain birth weight more quickly and to exhibit larger average daily weight gains than those reported by Dancis et al.² The authors of these studies suggested that improvements in preterm formulas and an increased use of total PN supported more rapid growth and that their curves

Fig 7. Average body weight versus postmenstrual age in weeks for all study infants with gestational ages 24 to 25 weeks (dotted line), 26 to 27 weeks (short dashes), and 28 to 29 weeks (long dashes). The reference intrauterine growth curves were plotted using the smoothed 10th and 50th percentile birth weight data reported by Alexander et al.²²



were a reflection of changes in hospital nutritional management.

With current NICHD Neonatal Research Network Center nutritional practices, we found that once VLBW infants regain birth weight, their average daily weight gain ranged between 14.4 and 16.1 g/kg body weight/d (Table 3), a rate similar to the reported intrauterine weight gain of $\sim 1.5\%/d$ or 15 g/kg/d.^{4,25,28,29} In addition, their average weekly increments in length (0.9 cm/wk) and HC (0.9 cm/wk) are similar to the rates of intrauterine length and HC increase reported by Lubchenco et al³⁰ between 26 and 36 weeks of gestation (1.1 cm/wk and 0.7 cm/wk, respectively). Also, their average weekly increment in MAC (0.35 cm/wk) is similar to the average weekly intrauterine MAC increase reported by Sasanow et al¹⁶ for infants between 25 and 36 weeks of gestation (0.34 cm/wk); the MAC reflects deposition of fat and muscle stores. We noted statistically significant, positive correlations between body weight, length, HC, and MAC increments.

Nonetheless, although the rate of weight gain that we observed after birth weight was regained was similar to the reported intrauterine rate, as seen in Fig 7, most of the infants born between 24 and 29 weeks of gestation would not have achieved the median birth weight of the reference fetus of the same postmenstrual age at hospital discharge. In fact, because many VLBW infants are discharged when they reach 35 completed weeks and a body weight of ~ 2000 g, they are less than the 10th percentile birth weight (2159 g) for 35 completed weeks of gestation according to the intrauterine growth data reported by Alexander et al.²² This observation has been previously described.^{4,31} Furthermore, because infants who experience common neonatal morbidities regained birth weight later and gained body weight more slowly than infants without neonatal morbidities (Fig 5), the body weight at 35 weeks postmenstrual age for infants with morbidities

would be even further below the median birth weight of a reference infant of similar postmenstrual age. The magnitude of this deficit reflects the increased time to regain birth weight and to achieve full enteral feedings. Since Hack et al³² reported that subnormal HC at 8 months corrected age is associated with poor cognitive function at school age, an additional concern for these infants would be persistently slow postnatal head growth.

Although our study did not specify nutritional practices, we found several associations that should be examined further. Infants who were started on enteral nutrition at or before the median age gained weight faster than if feedings were started after the median age. This finding is consistent with several studies³³⁻³⁶ suggesting that early minimal enteral feedings decreases the time required to reach full enteral nutrition. However, within each 200-g birth weight interval, we found no correlation between the age at the first enteral feeding and the age at which full enteral feedings was achieved. We also observed that infants gained weight faster if they achieved full enteral nutrition earlier or if they received 75% or more of their total daily fluid volume as PN for a shorter duration. Unfortunately, such associations may be confounded by management decisions to initiate enteral feedings earlier in healthier infants and later in sicker infants. Similar observations were made by Wright et al.⁶

We also noted that infants with major morbidities gained weight more slowly than infants without morbidities (Fig 5). Poorly nourished infants who are gaining weight slowly might be more prone to develop CLD and late-onset sepsis.³⁷ However, the incidence of morbidities might be decreased by identifying infants in whom the average time to regain birth weight or to reach full enteral nutrition is delayed (Table 2), and then changing their nutritional management, such as increasing the dietary protein/energy ratio. This is a testable hypothesis. Recent

observations comparing nutritional practices and weight gain by VLBW infants cared for at seven regional neonatal intensive care units demonstrated that the presence of a neonatal nutritionist on the health care team was associated with significantly greater weight-adjusted growth.³⁸

The strength of our data lie in the large, heterogeneous population of VLBW infants studied. It is limited by the lack of data describing daily caloric and nutritional intake. Therefore, growth could not be correlated with nutritional intake. Nonetheless, the infants' management reflects current nutritional practices because the mean ages at which full enteral feeding were achieved and at which birth weights were regained for infants with birth weights ≤ 1000 g (Table 2) were similar to the recent report by Pauls et al.⁸

CONCLUSIONS

In summary, we have prospectively collected longitudinal data on a large population of infants with birth weights 501 to 1500 g who have been managed with current nutritional practices. Postnatal growth curves were constructed from anthropometric measures (Figs 1 to 4). Most VLBW infants did not achieve catch-up growth during the neonatal intensive care unit hospitalization when compared with the median birth weight of a reference fetus of the same postmenstrual age (Fig 7). Infants with morbidities gained weight more slowly than infants without morbidities (Fig 5). The rate of weight gain was also associated with the duration that infants received at least 75% of their total daily fluid volume as PN, the age at which enteral feedings were initiated and the age at which full enteral feedings were achieved. These growth curves (Figs 1 to 4) should not be taken as optimal. They may be used to better understand postnatal growth, to identify infants developing illnesses that affect growth, and to aid in designing future research. Randomized clinical trials should be performed to evaluate whether different nutritional management practices will permit birth weight to be regained earlier and result in more rapid weight gain, more appropriate body composition, and improved short and long-term outcomes.

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REFERENCES

- Bauer K, Bovermann G, Roithmaier A, Gotz M, Proiss A, Versmold H. Body composition, nutrition, and fluid balance during the first two weeks of life in preterm neonates weighing less than 1500 grams. *J Pediatr.* 1991;118:615-620
- Dancis J, O'Connell JR, Holt LE Jr. A grid for recording the weight of premature infants. *J Pediatr.* 1948;33:570-572
- Brosius KK, Ritter DA, Kenny JD. Postnatal growth curve of the infant with extremely low birth weight who was fed enterally. *Pediatrics.* 1984;74:778-782
- Gill A, Yu VYH, Bajuk B, Astbury J. Postnatal growth in infants born before 30 weeks' gestation. *Arch Dis Child.* 1986;61:549-553
- Shaffer SG, Quimiro CL, Anderson JV, Hall RT. Postnatal weight changes in low birth weight infants. *Pediatrics.* 1987;79:702-705
- Wright K, Dawson JP, Fallis D, Vogt E, Lorch V. New postnatal growth grids for very low birth weight infants. *Pediatrics.* 1993;91:922-926
- Berry MA, Conrod H, Usher RH. Growth of very premature infants fed intravenous hyperalimentation and calcium-supplemented formula. *Pediatrics.* 1997;100:647-653
- Pauls J, Bauer K, Versmold H. Postnatal body weight curves for infants below 1000 g birth weight receiving early enteral and parenteral nutrition. *Eur J Pediatr.* 1998;157:416-421
- Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institutes of Child Health and Human Development Neonatal Network. *Pediatrics.* 1991;87:587-597
- Hack M, Wright LL, Shankaran S, et al. Very-low-birth-weight outcomes of the National Institutes of Child Health and Human Development Neonatal Network, November 1989 to October 1990. *Am J Obstet Gynecol.* 1995;172:457-464
- Fanaroff AA, Wright LL, Stevenson DK, et al. Very-low-birth-weight outcomes of the National Institutes of Child Health and Human Development Neonatal Research Network, May 1991 through December 1992. *Am J Obstet Gynecol.* 1995;173:1423-1431
- Arbuckle TE, Wilkins R, Sherman GJ. Birth weight percentiles by gestational age in Canada. *Obstet Gynecol.* 1993;81:39-48
- Walsh MC, Kleigman RM. Necrotizing enterocolitis: treatment based staging criteria. *Pediatr Clin North Am.* 1986;33:179-201
- Papile L-A, Burstein J, Burstein J, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr.* 1978;92:529-534
- Fomon SJ, Nelson SE. Size and growth. In: Fomon SJ, ed. *Nutrition of Normal Infants.* St. Louis, MO: Mosby-Year Book, Inc, 1993:36-84
- Sasanow SR, Georgieff MK, Pereira GR. Mid-arm circumference and mid-arm/head circumference ratios: standard curves for anthropometric assessment of neonatal nutritional status. *J Pediatr.* 1986;109:311-315
- Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics.* 1982;38:963-974
- Smith PL. Splines as a useful convenient statistical tool. *American Statistician.* 1979;33:57-62
- Littell R, Milliken G, Stroup WW, Wolfinger R. *SAS System for Mixed Models.* Cary, NC: SAS Institute Inc; 1996
- Ng PC. The effectiveness and side effects of dexamethasone in preterm infants with bronchopulmonary dysplasia. *Arch Dis Child.* 1993;68:330-336
- Papile L-A, Tyson JE, Stoll BJ, et al. A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. *N Engl J Med.* 1998;338:1112-1118
- Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. *Obstet Gynecol.* 1996;87:163-168
- American Academy of Pediatrics, Committee on Nutrition. Nutritional needs of low-birth-weight infants. *Pediatrics.* 1977;60:519-530

24. American Academy of Pediatrics, Committee on Nutrition. Nutritional needs of low-birth-weight infants. *Pediatrics*. 1985;75:976-986
25. Lubchenco LO, Hansman C, Dressler M, Boyd E. Intrauterine growth as estimated from liveborn birth weight data at 24 to 42 weeks of gestation. *J Pediatr*. 1963;32:793-800
26. Usher R, McLean F. Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. *J Pediatr*. 1969;74:901-910
27. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *Am J Obstet Gynecol*. 1976;126:555-564
28. Sparks JW. Human intrauterine growth and nutrient accretion. *Semin Perinatol*. 1984;8:74-93
29. Jackson AA, Shaw JCL, Barber A, Golden MHN. Nitrogen metabolism in preterm infants fed human donor breast milk: the possible essentiality of glycine. *Pediatr Res*. 1981;15:1454-1461
30. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics*. 1966;37:403-408
31. Lucas A, Gore SM, Cole TJ, et al. Multicentre trial on feeding low birthweight infants: effects of diet on early growth. *Arch Dis Child*. 1984;59:722-730
32. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med*. 1991;325:231-237
33. Dunn L, Hulman S, Weiner J, Kleigman R. Beneficial effects of early hypocaloric enteral feeding on neonatal gastrointestinal function: preliminary report of a randomized trial. *J Pediatr*. 1988;112:622-629
34. Slagle TA, Gross SJ. Effect of early low-volume enteral substrate on subsequent feeding tolerance in very low birth weight infants. *J Pediatr*. 1988;113:526-531
35. Berseth CL. Minimal enteral feedings. *Clin Perinatol*. 1995;22:195-205
36. Tyson JE, Kennedy KA. Minimal enteral nutrition in parenterally fed neonates. In: Sinclair J, Bracken M, Soll RF, Hobar JD, eds. *Neonatal Module of the Cochrane Database of Systematic Reviews*. Update Software. Oxford, London, England: BMJ Publishing Group; The Cochrane Collaboration, Issue No. 1, 1998
37. Frank L, Sosenko IRS. Undernutrition as a major contributing factor in the pathogenesis of bronchopulmonary dysplasia. *Am Rev Respir Dis*. 1988;138:725-729
38. Rubin LP, Richardson DK, Bednarek FJ, Olsen I, McCormick MC, SNAP-II Study Group. Longitudinal growth in hospitalized VLBW infants: identification of patient characteristics and inter-NICU differences. *Pediatr Res*. 1997;41:239A.

THE HAND LEARNS TO SPEAK

The final proof that sign is a “natural language” comes from the work of Laura Ann Petitto at McGill University in Montreal. In a groundbreaking series of observations and experiments, she has shown that deaf children acquire sign in the same graduated manner, and on precisely the same timetable, as hearing children acquire speech. Furthermore, among bilingual deaf children who are unimodal (two different languages, both in sign) and bimodal (one language signed, the other spoken), the developmental profiles for the two languages are identical. Finally, Petitto found that in the extremely rare instances in which *hearing* children raised by deaf parents are taught sign as a native language, the processes and milestones parallel those observed in both deaf and hearing children.

Petitto L. On the autonomy of language and gesture: evidence from the acquisition of personal pronouns in American sign language. *Cognition*. 1987;1:1-62

Wilson FR. *The Hand*. New York, NY: Pantheon; 1998

Submitted by Student

Longitudinal Growth of Hospitalized Very Low Birth Weight Infants
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