BIRTH WEIGHT IN RELATION TO MORBIDITY AND MORTALITY AMONG NEWBORN INFANTS

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ABSTRACT

Background At any given gestational age, infants with low birth weight have relatively high morbidity and mortality. It is not known, however, whether there is a threshold weight below which morbidity and mortality are significantly greater, or whether that threshold varies with gestational age.

Methods We analyzed the neonatal outcomes of death, five-minute Apgar score, umbilical-artery blood pH, and morbidity due to prematurity for all singleton infants delivered at Parkland Hospital, Dallas, between January 1, 1988, and August 31, 1996. A distribution of birth weights according to week of gestation at birth was created. Infants in the 26th through 75th percentiles for weight served as the reference group. Data on preterm infants (those born at 24 to 36 weeks of gestation) were analyzed separately from data on infants delivered at term (37 or more weeks of gestation).

Results A total of 122,754 women and adolescents delivered singleton live infants without malformations between 24 and 43 weeks of gestation. Among the 12,317 preterm infants who were analyzed, there was no specific birth-weight percentile at which morbidity and mortality increased. Among 82,361 infants who were born at term and whose birth weights were at or below the 75th percentile, however, the rate of neonatal death increased from 0.03 percent in the reference group (26th through 75th percentile for weight) to 0.3 percent for those with birth weights at or below the 3rd percentile ($P<0.001$). The incidence of five-minute Apgar scores of 3 or less and umbilical-artery blood pH values of 7.0 or less was approximately doubled for infants at or below the 3rd birth-weight percentile ($P=0.003$ and $P<0.001$, respectively). The incidence of intubation at birth, seizures during the first day of life, and sepsis was also significantly increased among term infants with birth weights at or below the 3rd percentile. These differences persisted after adjustment for the mother's race and parity and the infant's sex.

Conclusions Mortality and morbidity are increased among infants born at term whose birth weights are at or below the 3rd percentile for their gestational age. (N Engl J Med 1999;340:1234-8.)

EACH year in the United States, approximately 250,000 infants are born weighing less than 2500 g. These infants are classified as having low birth weight.[1] Although the majority of these infants are born before term, approximately 40,000 are born at term according to National Institutes of Health estimates, having suffered intrauterine growth retardation.[2]

In 1963 Lubchenco and coworkers[3] published detailed birth-weight nomograms according to gestational week. Small-for-gestational-age infants were subsequently defined as those whose weights were below the 10th percentile for their gestational ages.[4] These infants were found to be at increased risk for neonatal death. For example, the neonatal mortality rate for small-for-gestational-age infants born at 38 weeks of gestation was 1 percent, as compared with 0.2 percent for those with appropriate birth weights. Not all infants with birth weights below the 10th percentile have pathologic growth retardation, however; some are small simply because of maternal constitutional factors.[5,6]

Although the concept of abnormal fetal growth is basic to modern ideas of perinatal medicine, there is limited information concerning the birth-weight threshold for a given gestational age at which morbidity and mortality increase significantly. For example some advocate the use of the 10th percentile as such a threshold value,[4] whereas others recommend the 5th,[7] 3rd,[8] or 15th[9] percentile. We undertook this study to determine the birth-weight thresholds, for both preterm and term infants, associated with a significant increase in adverse neonatal outcomes. The birth-weight distribution used was specific to the study population. Between 1988 and 1996, approximately 127,000 infants were delivered at our hospital. The availability of data from this cohort permitted us to derive a population-based birth-weight nomogram and then to assess the birth-weight thresholds at which the well-being of newborn infants might be compromised.

METHODS

Study Population

Selected obstetrical and neonatal outcomes for all women delivering infants at Parkland Hospital in Dallas are routinely en-

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tered into a computerized data base. Nurses attending each delivery complete an obstetrical data sheet, and research nurses assess the data for consistency and completeness before electronic storage. Data on infants' outcomes are abstracted from discharge records. Parkland Hospital is a tax-supported institution serving Dallas County. The obstetrics service is staffed by house officers and faculty members of the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical School.

Between January 1, 1988, and August 31, 1996, a total of 126,680 women and adolescents delivered infants at the hospital, of whom 122,754 were live-born singleton infants without malformations and with gestational ages of 24 weeks or more. Infants delivered at less than 24 weeks of gestational age were excluded from our study because their intrapartum management was influenced by concern about viability. Stillbirths were excluded because the gestational age at which fetal growth ceased could not be precisely determined, since delivery, and thus measurement of birth weight, often occurred days to weeks after fetal death. Ninety-seven percent of the mothers received prenatal care, averaging eight visits, in our hospital system. Approximately 60 percent were enrolled for prenatal care in the first trimester, and 90 percent enrolled before the end of the second trimester.

Gestational Age

For the purpose of this study, the obstetrical estimate of gestational age that was used to manage the care of the women and adolescents during the intrapartum period was also used to create a distribution of birth weights for each gestational week. This estimate was based on the date of the last menstrual period and the results of obstetrical ultrasonography, if any, performed during the pregnancy. The reported time of the last menstrual period was accepted as correct if the fundal height measured between 18 and 30 weeks of gestation was correlated with the week of gestation within 2 cm.[10] Subjects with discrepancies between the two values underwent obstetrical ultrasonography.

The validity of the obstetrical estimate of gestational age based on the menstrual history was assessed by two separate methods. First, a cohort of 34,475 women and adolescents who underwent antepartum ultrasonography was identified. These subjects did not differ significantly from the total study population with regard to age, race, or parity. The correlation coefficient for the estimate of gestational age based on ultrasonography and the obstetrical estimate of gestational age based on the last menstrual period was 0.9. The mean (±SD) gestational age at the time of ultrasonography was 25±7 weeks. Similarly, the correlation coefficient for the obstetrical estimate of gestational age and the pediatrician's assessment of the gestational age of the newborn infant was 0.7. In 108,493 women (88 percent), the obstetrical estimate and the pediatrician's estimate were within two weeks of each other. (The obstetrical estimates of gestational age were available to the pediatricians.)

Birth Weight

The distributions of birth weights for each completed week of gestation were examined for statistical normality, and smoothed birth-weight curves were derived for each percentile.[11] For example, 38 completed weeks of gestation included 38 weeks, 0 days, through 38 weeks, 6 days. Six categories of birth-weight percentile were selected for study: the 3rd or below, 4th through 5th, 6th through 10th, 11th through 15th, 16th through 25th, and 26th through 75th percentiles. Infants whose birth weights fell in the 26th through 75th percentiles were used as the reference group.

Outcome Measures

The outcomes we studied included death up to 28 days of age, an Apgar score of 3 or less at five minutes, and an umbilical-artery blood pH of 7.0 or less. The latter two measurements assessed characteristics attributable to the condition of the infant at birth. Umbilical-cord blood was obtained from all infants for measurement of pH. In infants born at term, morbidity was defined as the onset of seizures in the first 24 hours after birth or the need for intubation in the delivery room. In preterm infants, morbidity was defined as respiratory distress (the need for ventilator therapy in the first 24 hours after birth); intraventricular hemorrhage, grade 3 or 4; necrotizing enterocolitis requiring surgery; or sepsis. The diagnosis of sepsis required a positive blood culture.

Statistical Analysis

Smoothed curves for birth-weight percentiles according to gestational age were derived for the entire cohort. Similar curves were also constructed according to the mother's race and parity and the infant's sex. Univariate analysis of infants' outcomes according to birth-weight percentile was performed with use of chi-square statistics. The estimates and significance levels were adjusted for the mother's race and parity and the infant's sex by the Cochran–Mantel–Haenszel method. Bonferroni corrections were used in cases of multiple testing. All P values are two-sided.

RESULTS

Of the women and adolescents whose pregnancy outcomes are described in this report, 54 percent (65,712) were Hispanic, 28 percent (34,872) were black, 15 percent (18,616) were white, and 3 percent (3554) were of other racial or ethnic backgrounds. The mean maternal age was 24±6 years; 3 percent were under the age of 16 years and 4 percent were 35 years old or older. A total of 45,937 (37 percent) were nulliparous.

Data on 122,754 singleton infants without malformations (12,317 preterm infants and 110,437 term infants) were available for analysis. Of these, 91,580 infants (9219 preterm infants and 82,361 term infants) had birth weights at or below the 75th percentile. The infants' outcomes, according to birth-weight percentile, were analyzed separately for those delivered at 36 weeks or less of gestation (preterm birth) and those delivered at 37 weeks or more (birth at term).

Preterm Infants

Selected outcomes for the 9219 preterm infants with birth weights at or below the 75th percentile are shown according to birth-weight category in Table 1. The presence or absence of severe fetal acidemia (umbilical-artery blood pH, 7.0 or less), necrotizing enterocolitis, and sepsis was not related to birth-weight category. The incidence of grade 3 or 4 intraventricular hemorrhage, however, was significantly increased among preterm infants in the smallest birth-weight category. Grade 3 or 4 intraventricular hemorrhage was diagnosed in 3.2 percent of infants at or below the 3rd percentile for birth weight, as compared with 1.5 percent in the reference group of infants in the 26th through 75th percentiles ($P=0.01$). The incidence of respiratory distress requiring ventilator therapy was significantly increased among infants in each of the birth-weight percentiles below the 26th percentile, as compared with the reference group (Table 1).

Table 1. Outcomes of Live-Born Singleton Preterm Infants (Born at 24 to 36 Weeks of Gestation) in Relation to Birth-Weight Percentile.

Outcome	Birth-Weight Percentile					
	≤3rd (N=378)	4th–5th (N=247)	6th–10th (N=635)	11th–15th (N=613)	16th–25th (N=1240)	26th–75th (N=6106)
	number (percent)					
Umbilical-artery blood pH ≤7.0	5 (1.3)	5 (2.0)	8 (1.3)	5 (0.8)	10 (0.8)	52 (0.9)
Grade 3 or 4 intraventricular hemorrhage	12 (3.2)*	6 (2.4)	12 (1.9)	15 (2.4)	28 (2.3)	93 (1.5)
Respiratory distress requiring ventilation in first 24 hr	85 (22.5)*	47 (19.0)*	134 (21.1)*	117 (19.1)*	226 (18.2)*	768 (12.6)
Necrotizing enterocolitis requiring surgery	4 (1.1)	1 (0.4)	3 (0.5)	5 (0.8)	9 (0.7)	34 (0.6)
Sepsis (positive blood culture)	8 (2.1)	4 (1.6)	9 (1.4)	4 (0.7)	19 (1.5)	72 (1.2)
Death in first 28 days	26 (6.9)*	8 (3.2)	26 (4.1)*	15 (2.4)	37 (3.0)*	124 (2.0)

*P<0.05 for the comparison with the infants with birth weights in the 26th through 75th percentiles for gestational age.

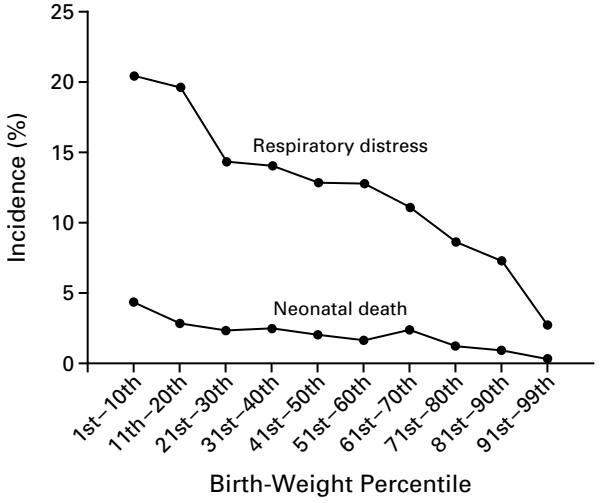

Figure 1. Incidence of Respiratory Distress and Neonatal Death among 12,317 Preterm Infants (Born at 24 to 36 Weeks of Gestation), According to Birth-Weight Percentile.

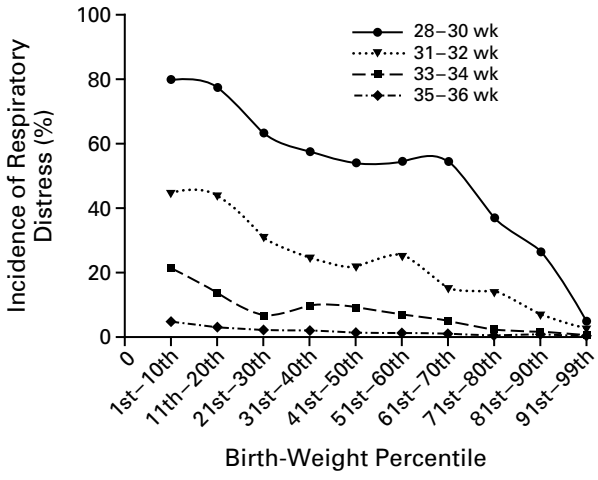

Figure 2. Incidence of Respiratory Distress among 12,317 Preterm Infants, According to Birth-Weight Percentile after Stratification According to Gestational Age (28 through 30 Weeks, 31 or 32 Weeks, 33 or 34 Weeks, and 35 or 36 Weeks).

Because the incidence of respiratory distress was significantly higher in all the birth-weight percentiles below the 26th percentile than in the reference group, we expanded the analysis to include all possible birth-weight percentiles (Fig. 1). The incidence of respiratory distress increased as the birth-weight percentile decreased. Analysis of the data after stratification according to gestational-age groups revealed an increasing incidence of respiratory distress associated with both lower gestational age and lower birth-weight percentile (Fig. 2). As we did with respiratory distress, we expanded the analysis of neonatal death to encompass all birth-weight percentiles (Fig. 1). Neonatal death rates among preterm infants were proportional to fetal weight across the entire spectrum of birth-weight percentiles. The birth-weight–percentile thresholds for a significantly increased risk of respiratory distress and neonatal death among preterm infants were also analyzed with adjustment for the mother's race and parity and the infant's sex. No specific birth-weight threshold was significantly associated with either of these outcomes.

TABLE 2. OUTCOMES OF LIVE-BORN SINGLETON TERM INFANTS (BORN AT ≥37 WEEKS OF GESTATION) IN RELATION TO BIRTH-WEIGHT PERCENTILE.

OUTCOME	BIRTH-WEIGHT PERCENTILE					
	≤3RD (N=3184)	4TH–5TH (N=2065)	6TH–10TH (N=5254)	11TH–15TH (N=5400)	16TH–25TH (N=10,857)	26TH–75TH (N=55,601)
	number (percent)					
Apgar score ≤3 at 5 min	7 (0.2)*	1 (<0.1)	6 (0.1)	5 (0.1)	9 (0.1)	38 (0.1)
Umbilical-artery blood pH ≤7.0	28 (0.9)*	12 (0.6)	28 (0.5)	27 (0.5)	37 (0.3)	212 (0.4)
Intubation in delivery room	70 (2.2)*	11 (0.5)	39 (0.7)	39 (0.7)	70 (0.6)	317 (0.6)
Seizures during first 24 hr after birth	14 (0.4)*	4 (0.2)	14 (0.3)*	9 (0.2)	16 (0.1)	68 (0.1)
Sepsis (positive blood culture)	15 (0.5)*	6 (0.3)	12 (0.2)	15 (0.3)	28 (0.3)	125 (0.2)
Death in first 28 days	9 (0.3)*	2 (0.1)	2 (<0.1)	3 (0.1)	3 (<0.1)	18 (<0.1)

*P<0.05 for the comparison with the infants with birth weights in the 26th through 75th percentiles for gestational age.

Term Infants

Selected outcomes for 82,361 term infants in relation to their birth-weight percentiles are shown in Table 2. The analysis excluded 28,076 infants whose birth weights were above the 75th percentile. The percentage of infants with low five-minute Apgar scores was significantly higher among those at or below the 3rd birth-weight percentile (0.2 percent) than in the reference group (0.1 percent; P=0.003). Similarly, the incidence of severe fetal acidemia and the need for intubation in the delivery room was significantly higher among the infants in this group (P<0.001 for both outcomes). The incidence of seizures during the first 24 hours of life, a potential reflection of intrapartum stress, was significantly increased in two of the lowest birth-weight groups (those at or below the 3rd percentile, and those in the 6th through the 10th percentiles). The rates of incidence of sepsis and neonatal death were also significantly increased among infants at or below the 3rd percentile. In fact, the incidence of neonatal death was almost 10 times as high among infants with birth weights at or below the 3rd percentile as in the reference group (0.3 percent vs. 0.03 percent, P<0.001).

The data set was also analyzed with adjustment for the infant's sex and the mother's race. The 3rd-percentile birth-weight threshold for increased morbidity and mortality (Table 2) remained significant when the data were analyzed according to these demographic factors. Similarly, parity did not significantly influence the birth-weight thresholds for adverse neonatal outcomes.

DISCUSSION

The threshold birth-weight percentile for infant mortality and for most indexes of morbidity that appears to define the boundary between normal and abnormal fetal growth is more readily apparent among term infants than among preterm infants. Morbidity and mortality were significantly higher among term infants who were at or below the 3rd percentile of weight for their gestational age. In contrast, there was no specific birth-weight threshold for neonatal morbidity or mortality among preterm infants. Indeed, the risk of adverse outcomes, such as respiratory distress and neonatal death, increased continuously with decreasing birth-weight percentiles among preterm infants.

There have been few reports describing birth-weight thresholds for adverse infant outcomes. The earliest such report[4] linked neonatal death to birth weight at the 10th percentile. For more than 30 years, this percentile has been defined as the threshold for clinically important fetal growth restriction. Manning[5] also defined the 10th percentile as the threshold for elevated neonatal morbidity and mortality, manifested as birth asphyxia and abnormal neurologic development. However, all infants with birth weights above the 10th percentile were considered to be of appropriate size for their gestational age. We chose to analyze our results with birth weights at the 26th through 75th percentiles as the norm for fetal growth. Larger infants were excluded because they may have morbidity associated with excessive size. Manning described a continuum of increasing risk for adverse infant outcomes as birth weight decreased from the 10th to the 1st percentile for gestational age. On the basis of an analysis of 8719 births, Kramer and colleagues[12] also concluded that morbidity and mortality were continuously and inversely proportional to fetal growth. Neonatal outcomes related to suboptimal fetal growth are associated with adverse neurologic outcomes at two years of age.[13]

There have been several reports of accelerated fetal pulmonary maturation in association with intrauterine growth restriction, defined as a birth weight for gestational age that is below the 10th percentile. One explanation for this phenomenon is that the fetus responds to a stressful environment by increasing adrenal glucocorticoid production, which leads to accelerated fetal lung maturation.[14] Although this concept pervades modern thinking about perinatal medicine, there is considerable controversy as to whether the growth-restricted infant truly has an advantage with respect to the risk of respiratory distress. The results of our analysis of preterm infants, along with other recent reports,[15] challenge this concept of accelerated maturation. We could not identify a specific fetal-growth threshold for respiratory disease; instead, we found that the incidence of respiratory distress was inversely proportional to the birth-weight percentile. However, respiratory distress was also significantly associated with gestational age among preterm infants. We therefore analyzed the incidence of respiratory distress at all birth-weight percentiles in relation to gestational age; the incidence of respiratory disease was directly related to both the birth-weight percentile and gestational age. In other words, morbidity among preterm infants is influenced by both fetal growth and fetal age. The same relations were not found among term infants, in whom the effects of suboptimal fetal growth appear to be limited to the most severely undergrown infants. The effects of suboptimal fetal growth persisted after adjustment for the mother's race and parity and the infant's sex.

When is fetal growth suboptimal, or how small is too small? Our results suggest that for term infants, the answer is the 3rd birth-weight percentile. For preterm infants, the effects of suboptimal fetal growth are intensified by immaturity, making it difficult to discern a fetal-growth threshold that clearly identifies growth-restricted infants who are at increased risk for illness and death.

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