Birth Weight and Perinatal Mortality: The Effect of Gestational Age

Allen J. Wilcox, MD, PhD, and Rolv Skjærven, PhD

ABSTRACT

Background. The strong association between birth weight and perinatal mortality is due both to gestational age and to factors unrelated to gestational age. Conventional analysis obscures these separate contributions to perinatal mortality, and overemphasizes the role of birth weight. An alternative approach is used here to separate gestational age from other factors.

Methods. Data are from 400 000 singleton births in the Norwegian Medical Birth Registry. The method of Wilcox and Russell is used to distinguish the contributions to perinatal mortality made by gestational age and by relative birth weight at each gestational age.

Results. Gestational age is a powerful predictor of birth weight and perinatal survival. After these effects of gestational age are controlled for, relative birth weight retains a strong association with survival.

Conclusions. Current public health policies in the United States emphasize the prevention of low birth weight. The present analysis suggests that the prevention of early delivery would benefit babies of all birth weights. (*Am J Public Health.* 1992;82:378–382)

Introduction

Birth weight is the single strongest predictor of infant survival. However, its position in the causal pathway is unclear. One determinant of birth weight is gestational age: as the fetus matures, it grows. Some of the association of weight with survival presumably reflects this maturation. There is additional variability in weight that is unexplained by gestational age. This second type of birth weight variability is also strongly related to infant survival, but by biological mechanisms less well understood. The purpose of this paper is to separate mortality as related to gestational age from mortality as related to relative birth weight within fixed gestational age. In the process of such a separation, factors related to gestational age can be separated from other factors that contribute to perinatal mortality. This produces a picture of mortality that is different from the traditional weight-versus-age multivariate approach, a picture which may better reflect the underlying causal pathways.

Methods

Data are from the Medical Birth Registry of Norway, which includes all live births and fetal deaths after 16 weeks of gestation registered in Norway since 1967. We selected all singleton first births through 1984 with gestational ages of 28 or more weeks, totaling 413 051. Birth weights were grouped into 100-g categories, and gestational ages were grouped by completed weeks since last menstrual period. Birth weight data were missing for 0.2% of births and gestational age was missing for an additional 4.3%. Those births were excluded, leaving 394 386 births (Table 1). We defined perinatal mortality as fetal deaths plus deaths in the first week of life. Total perinatal mortality in this study group was 12.9 per thousand.

Our method of analysis adjusts for birth weight with the modified form of direct standardization suggested by Wilcox and Russell.[1,2] The modification is first to adjust all birth weights to a z-score scale. (A z score expresses birth weight in standard-deviation units relative to mean weight.) This z scale is based on the underlying Gaussian distribution of births in each group being compared. Standardization is carried out on the z scale of birth weight rather than on a scale of absolute birth weight. Such an approach allows the comparison of mortality for babies of the same *relative* weight (that is, relative to the Gaussian distribution of weight for the particular group), rather than for babies of the same absolute weight. When applied to an analysis of gestational age, this method identifies babies that are relatively small or large for their gestational age and compares them with babies of the same relative size at other gestational ages.

We estimate the z scale by fitting a Gaussian curve to the birth weight distri-

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Allen J. Wilcox is with the Epidemiology Branch of the National Institute of Environmental Health Sciences, Research Triangle Park, NC. Rolv Skjærven is with the Section for Medical Informatics and Statistics, University of Bergen, Bergen, Norway.

Requests for reprints should be sent to Allen J. Wilcox, MD, PhD, Epidemiology Branch, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, or to Rolv Skjærven, PhD, Section for Medical Informatics and Statistics, University of Bergen, Bergen, Norway.

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bution within each gestational age stratum. Figure 1 shows the distribution of birth weights in each stratum. Birth weight distributions between 38 and 46 weeks are almost exactly Gaussian. Below 38 weeks, two systematic deviations from the Gaussian emerge. First, as gestational age decreases there are increasing numbers of small babies in the lower tail of the distribution, outside the Gaussian. Many of these are presumably pathological conceptuses, including macerated stillbirths who stopped growing some time before delivery. (At 28 to 31 weeks, the distribution in the lower tail is obscured by the grouping of births less than 1000 g.)

Second, there is an increasing number of relatively heavy births as gestational age decreases. This pattern has been frequently observed and is attributed to errors in measurement of gestational age.[3,4] Gestational age defined by last menstrual period can be in error for at least two physiologic reasons: the estimated gestation length can be too short when bleeding in early pregnancy is mistaken for the last menstrual period, or too long when conception follows an extended follicular phase. The excess of heavier babies at early gestational ages is thought to represent babies whose recorded age is shorter than their true gestational age, and who therefore actually belong in one of the heavier distributions occurring at later gestations. There is presumably some misclassification of gestational age in every stratum, but the unequal distribution of births among the strata makes misclassification more apparent in some strata than in others. A small rate of misclassification among the large numbers of births around term would produce a considerable excess of heavy babies among the small numbers born into the preterm groups.

Deviations from the Gaussian distribution cause some difficulties in estimating parameters of the underlying Gaussian. A FORTRAN program has been developed to estimate these parameters in the presence of excess small births.[5,6] (This program is available upon request.) The FORTRAN procedure was suitable for most gestational-age strata, but did not work well at gestations of less than 38 weeks owing to the excess of heavy births. In those cases we have fit a Gaussian curve more approximately to the modal region of each distribution and extrapolated a standard deviation from later strata (Figure 1). Parameters of the Gaussian distribution for each gestational age stratum are shown in Table 2.

TABLE 1—Distribution of Births and Deaths by Gestational Age, with Gestational-age–Specific Relative Risks for Perinatal Death (Relative to Births at 40 weeks) before and after Adjustment for Birth weight

Gestational Age (weeks)	All Births	Perinatal Deaths	Perinatal Mortality[a]	Relative Risk[b]	Birth-weight–adjusted Relative Risk
28–31	2834	1034	364.9	85	91
32–33	3231	612	189.4	44	45
34	2924	318	108.8	25	21
35	4692	283	60.3	14	12
36	7824	285	36.4	8.5	6.4
37	14 172	332	23.4	5.4	4.2
38	30 254	370	12.2	2.8	2.3
39	67 970	411	6.0	1.4	1.3
40	104 126	450	4.3	**1.0**	**1.0**
41	88 946	467	5.3	1.2	1.2
42	46 457	301	6.5	1.5	1.6
43	12 810	128	10.0	2.3	2.4
44	4692	59	12.6	2.9	3.0
45	2332	29	12.4	2.9	2.6
46+	1122	10	8.9	2.1	2.1
Total	394 386	5089	12.9		

[a] Per 1 000 births.
[b] Relative to mortality at 40 weeks.

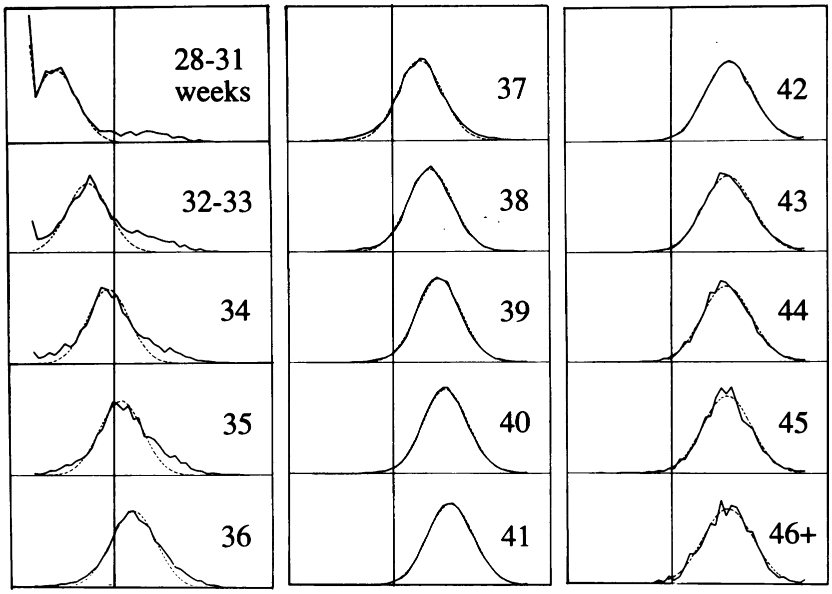

FIGURE 1—Frequency distributions of birth weight stratified by gestational age (solid curves), with underlying Gaussian distributions (dashed curves). A line at 2500 g is provided for reference.

Once parameters for each Gaussian were in hand, the mean and standard deviation for each gestational-age group were used to rescale birth weight to a z score. Weight-specific mortality rates for each group were also adjusted to the z scale in preparation for direct standardization. The choice of a distribution for the standard is not crucial. In general, the standard distribution should be similar to the actual distributions in the groups being analyzed. We chose a Gaussian distribution as our standard because it meets this criterion (Figure 1), but other distributions produce similar results. This standard distribution was applied to the weight-specific mortality rates for each gestational-age stratum. The risk of mortality for each gestational age was then expressed as a relative risk, with babies born at 40 weeks as the reference group.

TABLE 2—Gestation-specific Parameters of the Gaussian Birth Weight Distribution

Gestational Age weeks	Parameters of the Underlying Gaussian Mean, g	SD, g
28–31	1425	400
32–33	2010	400
34	2375	400
35	2610	415
36	2845	430
37	3050	430
38	3225	435
39	3380	430
40	3500	430
41	3595	440
42	3645	460
43	3605	470
44	3560	470
45	3560	465
46+	3585	480

Results

A strong gradient of risk was observed across gestational age after birth weights were adjusted to a *z* scale. Babies at the earliest stratum had a relative risk of 91 (Table 1). Relative risks calculated by this method are similar to those for gestational age unadjusted for birth weight.

The same results are presented graphically in Figures 2 and 3. First, weight-specific mortality rates for nine selected gestational-age strata are shown before adjustment to a *z* scale. (Mortality rates have been smoothed by grouping weight into 300-g categories.) These curves have the usual features of weight-specific mortality: rates are highest at the lowest birth weights, fall rapidly as birth weights increase, and then rise slightly at the highest birth weights.[7]

At lower weights, mortality rates are similar across the various gestational age groups, whereas at higher weights the rates tend to diverge. This pattern changes with adjustment of the birth weight scale. Figure 3 shows the identical mortality curves after birth weight has been converted to the *z* scale. Curves that formerly converged at the lower weights are now separate and roughly parallel over the whole range of birth weights. The distance between any two curves in Figure 3 represents the log of the relative risk associated with the corresponding difference in gestational age. The adjusted relative risks in Table 1 summarize the differences between the lowest mortality curve (at 40 weeks) and each of the other mortality curves in Figure 3.

Figure 4 inverts the display to show perinatal mortality risk by gestational age for babies at given *relative* birth weights. Thus, the top curve shows mortality rates for that high-risk group of babies who are four standard deviations below the mean weight for their gestational age. The next-to-bottom curve shows the mortality experience of babies who are at the mean weight for their gestational age. Within each birth weight group there is a strong gradient of mortality risk with gestational age, with the lowest risk occurring at 40 weeks.

Discussion

Growth is a natural part of the gestational maturation of the fetus. When we refer here to "gestational age" we mean not merely age itself but the tightly correlated phenomena of growth and maturation. Gestational age is a major contributor to birth weight, but it is only one of several contributors. There is another set of factors, less well understood, that produces variation in birth weight within each stratum of gestational age. Some authors attribute this variation entirely to the quality of fetal growth. We regard this interpretation as potentially misleading[8] and prefer the more neutral description "relative weight at each gestational age." This expression is a generalized form of the clinical terms "small for gestational age" or "large for gestational age."

The usual analysis of birth weight and gestational age finds that most of the association with mortality is through birth weight. This was well illustrated by Susser, Marolla, and Fleiss, who reported that when gestational age and weight are analyzed simultaneously, birth weight accounts for 90% of the variance of perinatal mortality, whereas gestational age accounts for barely 5%.[9]

Such conclusions are based on data in the form shown here in Figure 2. Arranged in this way, the mortality curves at different gestational ages are nearly indistinguishable across the lowest birth weights (where rates are highest). For example, babies at 2250 g have a similar risk of death whether their gestational age is 35 or 37 or 40 weeks (Figure 2). Although this analysis may seem to isolate the separate effects of gestational age and birth weight, it does not uncover the causal pathway. Susser and his colleagues were careful not to draw such conclusions, but these data have suggested to some that birth weight is fundamentally more important to survival than gestational age.[10]

If we compare babies of the same *relative* weight at each gestational age, a different picture emerges. Figure 3 shows mortality rates for babies at various relative weights (expressed as standard deviations from the mean at each gestational age). In effect, this compares all small-for-gestational-age babies (or all average-weight babies, or all large-for-gestational-age babies) across different gestational ages. Actual comparison of small-for-gestational-age mortality risks across gestational-age strata shows the same strong effect of gestational age on mortality.[11]

Babies of 2250 g have similar mortality risk regardless of gestational age. But these babies differ considerably in their relative size (Figure 3). At 35 weeks, a baby of 2250 g is about one standard de-

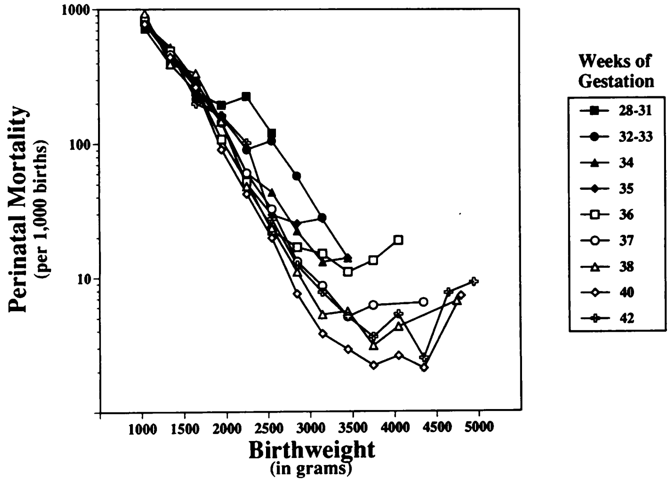

FIGURE 2—Weight-specific mortality rates for nine representative strata of gestational age.

viation below the Gaussian mean weight. At 37 weeks, a baby of that weight is about two standard deviations below the mean, and at 40 weeks it is about three standard deviations below the mean. (See circled points on Figure 3). The similar mortality risk of these three babies is the result of two opposing trends: relative size is worse, and gestational age is better.

The usual analytic methods, in which 2250-g babies are compared at different gestational ages, do not take into account the full benefit that would accrue to a preterm baby from extended gestation. Any strategy of prevention or intervention implicitly assumes that extended gestation is accompanied by fetal growth, that is, that a fetus' *relative* weight stays roughly the same as gestation advances. To measure the advantage of longer gestation, the survival of a 2250-g baby at 35 weeks should be compared with the survival of a baby who has grown at the expected rate in the interim. Such a comparison is accomplished by the adjustment to a relative birth weight scale. In Figures 3 and 4 the effects of relative size and gestational age are separated, showing the relationship of each to survival.

The parameters estimated for the Gaussian distributions of weight at the earlier gestational ages are subject to judgment. Even so, the uncertainty regarding parameters used for *z* scales is not crucial to the conclusion. As an illustration, births at 35 weeks had a relative risk of 12, compared with births at 40 weeks. If we vary the mean of the Gaussian distribution at 35 weeks by plus or minus 50 g, or the standard deviation by plus or minus 25 g, the relative risk for that stratum ranges from 11 to 13. Such a fluctuation is minor in comparison with the relative risk of 21 for 1 week earlier, or the relative risk of 6.4 for 1 week later.

More generally, the result here does not depend on a Gaussian distribution as the standard. Even a rectangular distribution produces nearly the same set of relative risks. This is because the mortality curves shown in Figure 3 are roughly parallel on the log scale, making the ratio of rates between any two gestational age groups approximately constant across the spectrum of birth weight. To the degree those ratios are constant, the choice of a distribution for standardization is inconsequential.[12] The central requirement for the method of standardization used here is that all data be compared on a scale of relative birth weight (the *z* scale), rather than on a scale of absolute birth weight.

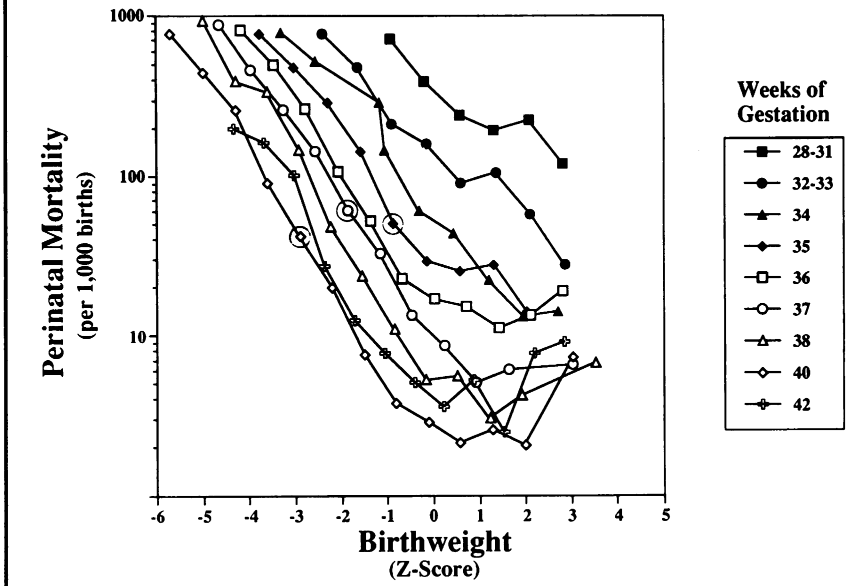

FIGURE 3—Z-score–specific mortality rates for nine representative gestational-age strata of births. (Circled points show mortality for 2250-g babies at different gestational ages. See text for discussion.)

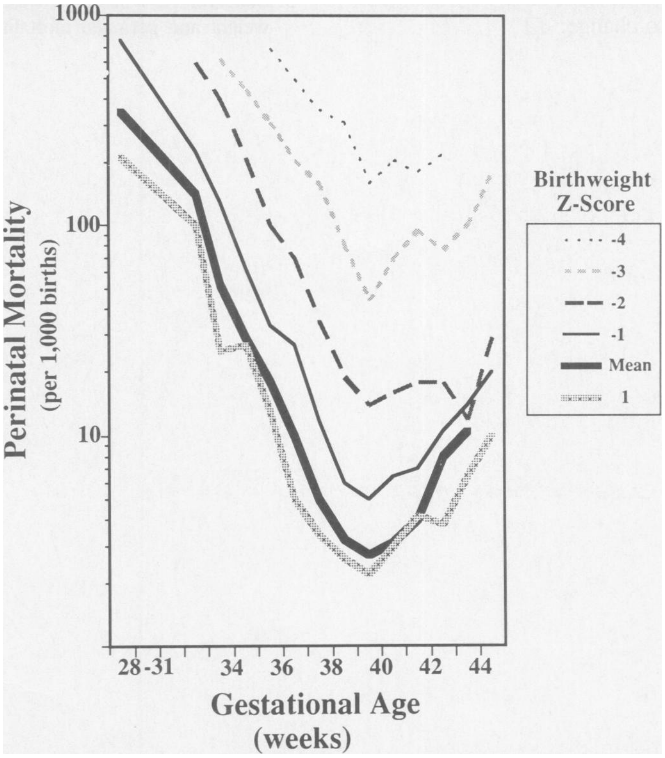

FIGURE 4—Gestational-age–specific mortality rates for babies stratified by relative size (in standard deviations from the Gaussian mean).

The present analysis highlights the importance of gestational age, and at the same time confirms a strong link between birth weight and perinatal mortality at each fixed gestational age. In his commentary on Wilcox and Russell's general approach, Peters stated that it was not possible to assess the "ultimate validity" of their model without considering gestational age.[13] Figure 3 shows that the relation between birth weight and perinatal mortality is not altered by stratifying on gestational age.

Gestational maturity has been understood for centuries to be important to infant survival. Still, gestational age tends to be slighted in contemporary US research.

This neglect may be due to a lack of clarity about the role of gestational age in the causal pathway. We have shown that there are two strong and separable factors affecting perinatal survival. One is gestational age, and the other is relative birth weight at any given gestational age. A baby can benefit as much from an increase in gestational age as from an increase in its weight relative to the weights of others at the same gestational age. This benefit of additional weeks of gestational age tends to be obscured by the customary multivariate methods of "controlling" for birth weight. There is a fallacy in inferring causality from a highly predictive relationship in a statistical model. The dominance of birth weight when the ordinary analytic methods are used may have contributed to the current emphasis on low birth weight as a public health problem.[14] Interventions aimed at increasing the size of babies may have little effect on perinatal mortality. Preterm delivery appears to be as worthy a target for public health intervention as low birth weight, and may be more amenable to change. □

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