Mortality Risk Among Preterm Babies

Immaturity Versus Underlying Pathology

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Background: Deaths among preterm births are presumably due to both immaturity and the conditions that cause preterm birth. Their relative contributions are unknown.

Methods: Using US birth certificates (1995–2002), we estimated what portion of preterm neonatal mortality may be attributable to immaturity alone. Twins have elevated mortality, yet they usually have lower mortality than singletons at most preterm weeks. Twinning itself is a cause of early birth. Thus, at any given preterm week, singletons are more likely than twins to have pathologic causes of preterm delivery. If any such cause is associated with a mortality risk higher than that conferred by twinning, it is possible for singletons to have higher mortality than twins at some preterm weeks. Thus, mortality of twins at those weeks comes closer to describing the risk due to immaturity itself. To exclude high-risk babies, we focused on singletons and twins least likely to have suffered fetal growth disruptions (ie, those with "optimal" birth weight). At each gestational week from 24 to 36, we identified (for twins and singletons separately) the 500-gram weight category with the lowest neonatal mortality, and selected the lower of the 2 mortality rates.

Results: Using the above as our best estimates of mortality due to immaturity alone, we calculated that about half the mortality of singleton preterm babies was due to the pathologies that cause early delivery.

Conclusions: Factors that cause preterm birth apparently contribute a large proportion of preterm mortality. If so, the prevention of preterm mortality requires more than the postponement of delivery.

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The high mortality of preterm babies comes from several sources. All preterm infants presumably experience some risk due to immaturity. In addition, some causes of preterm delivery may be dangerous in themselves. Thus, preterm babies can be at risk from both immaturity and the conditions that caused their preterm birth.[1–13] Although gestational-age-specific mortality rates before 37 weeks are often interpreted as reflecting immaturity, they are also driven by the contribution to mortality of the pathologies underlying preterm birth.

One piece of evidence in support of the heterogeneity of causes of death among preterm infants is the fact that gestational-age-specific mortality curves intersect when plotted for specific groups.[1,14] Twins and triplets, for example, have lower gestational-age-specific mortality than singletons during most of the preterm period (Fig. 1). As twinning itself increases the risk of mortality (and of preterm birth), the higher mortality of singleton preterm infants suggests that other causes of preterm birth are more dangerous than twinning.[1,7,8] Figure 2 illustrates this situation, with U representing one or more unmeasured causes of preterm birth that also directly causes mortality. In the figure, gestational age is a collider, ie, stratifying by gestational age creates an association between U and twinning. (An analogous scenario has been proposed to explain intersecting birth-weight-specific mortality curves.[15]) Under the conditions in Figure 2, a singleton born at any given preterm week will be more likely to be "pathologic" than a twin born preterm (as twinning could be the sole cause of preterm birth for some twins). If the pathology represented by U is associated with a mortality risk higher than the risk conferred by twinning, then it is possible for singletons to have higher mortality than twins at some preterm weeks. The same argument extends to triplets, whose risk of preterm birth (and mortality) is even higher than that of twins.

There is a growing awareness of the role of underlying pathology in preterm mortality and morbidity.[1–13] Preterm mortality due to immaturity alone is undoubtedly less than that estimated by empirical gestational-age-specific mortality rates–but how much lower? No previous effort has been made to quantify the survival probabilities of healthy fetuses delivered early (for example, because the mother—but not the fetus—was injured). This question could be addressed definitively by a random intervention to deliver healthy singletons prematurely—which is obviously not a feasible experiment. We attempt to provide a rough estimate of the contribution of immaturity alone and pathology (by "pathology," we mean both the effect of pathology and its potential interaction with immaturity) to singleton preterm mortality, using more indirect means.

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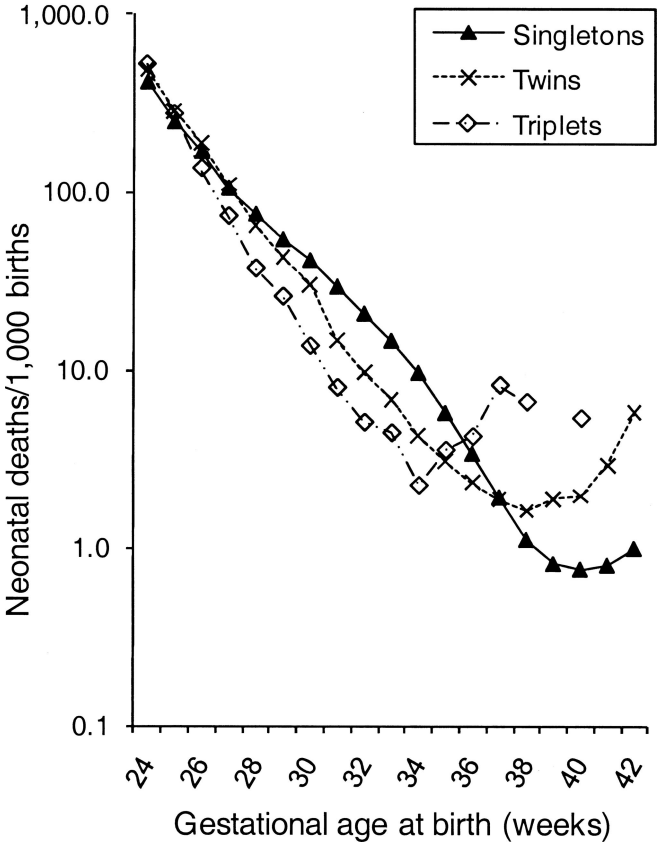

FIGURE 1. Gestational-age-specific neonatal mortality rates (per 1000 births) in singletons, twins, and triplets. Gestational age is a mixture of last menstrual period (LMP) and clinical estimates. Data from National Center for Health Statistics, US Live Births, 1995–2002.

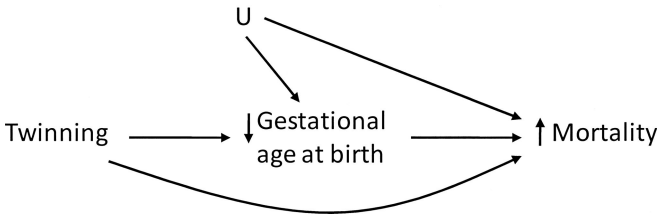

FIGURE 2. Graphic representation of the interrelation of twinning, mortality, and gestational age at birth, in the presence of a third factor, U, which decreases gestational age at birth and increases mortality. In this situation, gestational age is a collider, and the estimated effect of twinning on mortality will be altered when stratifying by gestational age, as such stratification creates a spurious relation between U and twinning.

METHODS

Data Source

We used data files from the National Center for Health Statistics, including all US live births and linked neonatal deaths (death within 28 days since birth) from 1995 through 2002. As we did not have information on deaths in 2003 for babies born in 2002, a small fraction of neonatal deaths will be missing for the December 2002 births.

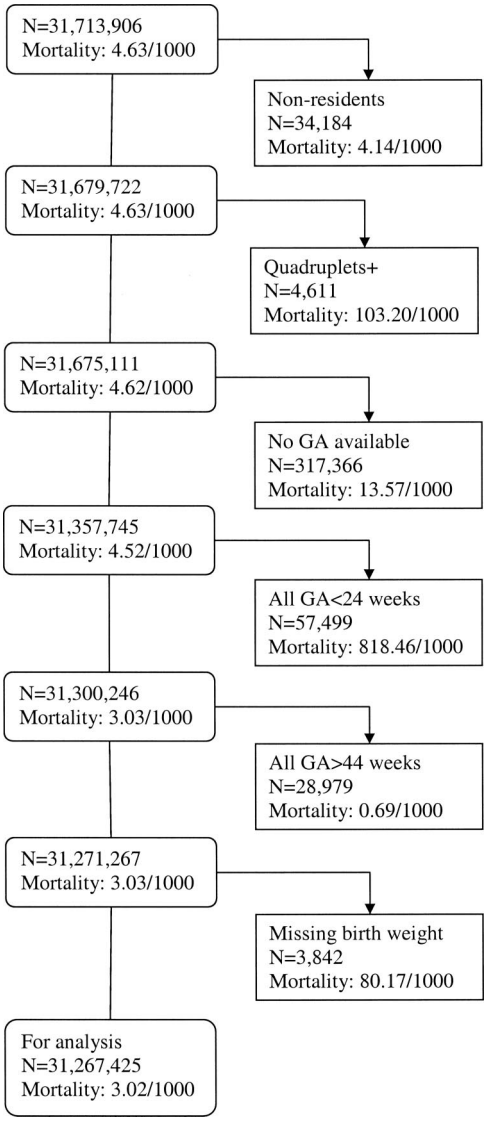

FIGURE 3. Steps to define the study population. GA indicates gestational age.

We excluded quadruplets and higher order multiples, babies born to non US-residents, those with missing gestational age or birth weight, and those born before 24 or after 44 weeks, leaving 31,247,865 babies for analysis (Fig. 3).

Correction of Gestational-Age Errors

Estimates of gestational age based on last menstrual period (LMP) are prone to error, particularly at preterm weeks.[16,17] With the exception of California, state birth certificates reported 2 measures of gestational age—one based on LMP and the other based on clinical assessment. Prior to carrying out our analysis, we developed a data-cleaning

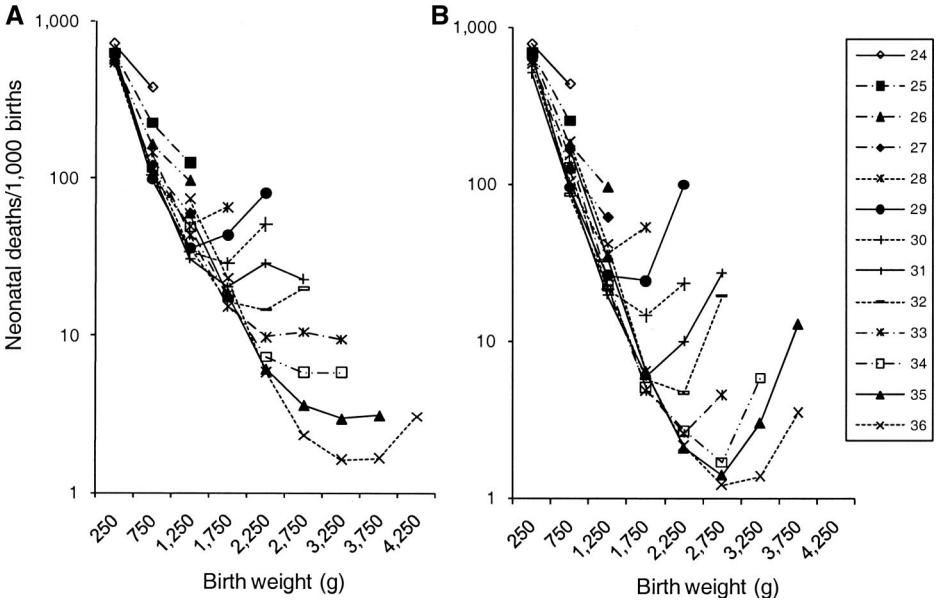

FIGURE 4. Weight-specific neonatal mortality of (A) singletons and (B) twins at gestational weeks 24–36. Data from National Center for Health Statistics, US Live Births, 1995–2002. Each point represents a 500-g category. Midpoint in the interval is marked.

algorithm to correct the most likely errors. Briefly, we relied on plausible concordance of birth weight and reported gestational age, requiring birth weights to be within either 3 or 4 standard deviations of the mean for each gestational age using external standards.[18] (The selection of standard-deviation criteria depended on which type of gestational-age measure was available, and how closely the measures agreed when they were both present.) We used the LMP estimate whenever possible, excluding or replacing the least credible LMP gestational ages with the clinical estimate. By favoring LMP, we limited situations in which the baby's condition may have influenced the clinical estimate of gestation. This procedure is reported in detail in the eAppendix (http://links.lww.com/EDE/A387).

Analysis

Based on the rationale given above, we assumed that, for at least some weeks, the neonatal mortality rates of preterm twins provided a better estimate of simple immaturity than the mortality rates of preterm singletons. We further attempted to identify a relatively "healthy" preterm group by focusing on babies least likely to have experienced fetal growth disruptions. Mortality declines as birth weight increases up to a certain weight, and then rises again at the heavier weights. The birth weight with the lowest mortality has been termed the "optimal" birth weight.[19] Although optimal birth weight is usually discussed for babies overall, there is also an optimal birth weight at each gestational age. As babies born preterm are generally smaller than those remaining in utero,[20,21] preterm babies with optimal birth weight could represent a less pathologic subgroup, free from the underlying conditions that affect fetal growth and increase mortality.[22–24] We plotted birth-weight-specific mortality rates (with birth weight in 500-g categories) at each gestational week between 24 and 36 for singletons and twins (Fig. 4). The weight category with the lowest mortality was identified as the optimal weight at that gestational age. (Despite their lower mortality within each week of gestation, even babies with optimal birth weight are likely to have pathologic conditions that prompted their early delivery.)

After selecting the more favorable mortality rate at each gestational age, we estimated the overall proportion of mortality due to immaturity alone by applying these rates to the observed distribution of preterm singleton births. Regardless of whether the rate came from twins or singletons, we assumed that this mortality rate was a better estimate of the risk faced by a healthy (but immature) singleton if it were randomly delivered at that gestational age. This generated an expected number of neonatal deaths at each gestational week, which we then summed across all preterm weeks to estimate the total expected rate of singleton preterm mortality due to immaturity alone. The difference between the observed and expected mortality rates among preterm infants provides a crude estimate of the mortality due to pathologic conditions of the fetus (as if all causes of preterm birth acted on mortality only through immaturity). We express this as a percent of total singleton neonatal mortality.

To explore how sensitive our results were to the chosen groups, we also calculated synthetic mortality rates based on different combinations of factors: (i) all singletons, twins, and triplets (regardless of birth weight), choosing the lowest of the 3 rates at each gestation) and (ii) only singletons at the optimal birth weight. In addition, we excluded infants for whom either placental abruption or incompetent cervix had been recorded.

RESULTS

Cleaning the gestational-age data excluded 0.2% of all births. In addition, we replaced LMP with clinical gestation in 10% of the babies who had both estimates. Misclassification of LMP was more likely among preterm births: among all babies with an LMP between 24 and 36 weeks for whom we had both estimates of gestation available, 29% were reclassified using the clinical estimate (27% were reclassified to a higher gestation). Substantially more singletons than twins or triplets were reclassified using the clinical estimate (33% of singletons, vs. 9.5% and 7.5% of twins and triplets, respectively). The present analysis is restricted to babies born between 24 and 36 weeks. This preterm group comprised 3,043,866 births (82.3% singletons, 16.2% twins, and 1.5% triplets).

Using the cleaned estimates of gestational age, 8% of singletons and 57% of twins were classified as preterm. Preterm mortality was 2.0% in singletons and 2.1% in twins. Without data cleaning, the neonatal mortality of babies born between 24 and 36 weeks based on LMP was 1.6% for singletons and 2.1% for twins.

Minimum Gestational-Age-Specific Mortality

Table 1 shows optimal birth weights and mortality rates for singletons and twins at each preterm gestational week between 24 and 36. The size of each cell varied among gestational weeks depending on the number within the 500 g birth weight category identified as "optimal."

Figure 5A shows optimal-weight mortality rates for singletons and twins at each gestational age. Twins contributed the lowest mortality at all weeks except the earliest (weeks 24, 25, and 27), where singletons had the lowest mortality. (The figures include the mortality rates for all singletons as visual reference.) This may suggest that virtually all babies (including twins) have underlying pathologies at these earliest weeks, allowing the inherently higher mortality of twins (potentially present at all gestations, all else being equal) to emerge.

After choosing the lesser of the 2 rates at each gestational age (Fig. 5B) and applying those mortality rates to all singleton preterm births, we obtained an estimated mortality due to immaturity of 9.98 per 1000 births. This is 51% of the total mortality for preterm babies, leaving 49% of preterm mortality as being due to effects (beyond immaturity) of pathologic conditions on the fetus (Table 2).

Other approaches gave somewhat different estimates. When based on the lowest gestational-age-specific mortality rates among singletons, twins, and triplets, the contribution of immaturity alone was estimated at 68% (driven mostly by the mortality rates of triplets). When the minimum calculated mortality was based on singletons at the optimal birth weight, the estimated proportion due to immaturity alone was 66%. When we excluded babies born to mothers with a record of placental abruption or incompetent cervix, none of the estimates changed by more than 1%. In all scenarios, the mortality rates at 24 weeks changed the least from the observed rate.

DISCUSSION

Preterm gestational-age-specific mortality rates reflect the mortality due to immaturity as well as the mortality due to pathologic conditions that also cause preterm birth. Immaturity and pathology are not mutually exclusive: immaturity no doubt exacerbates the effects of fetal pathology, and

TABLE 1. Number of Deaths and Births in the 500-g Category Representing Week-Specific Optimal Birth Weight

Week of Gestation	Singletons				Twins			
	No. Deaths	No. Births	Death Rate[a]	Optimum Weight (g)	No. Deaths	No. Births	Death Rate[a]	Optimum Weight (g)
24	8535	22,579	378.0	500–999	2319	5293	438.1	500–999
25	191	1522	125.5	1000–1499	1442	5661	254.7	500–999
26	595	6190	96.1	1000–1499	122	1272	95.9	1000–1499
27	847	14,242	59.5	1000–1499	215	3501	61.4	1000–1499
28	1129	22,789	49.5	1000–1499	228	6404	35.6	1000–1499
29	920	25,847	35.6	1000–1499	42	1733	24.2	1500–1999
30	619	21,749	28.5	1500–1999	85	5795	14.7	1500–1999
31	757	37,061	20.4	1500–1999	74	12,363	6.0	1500–1999
32	448	30,667	14.6	2000–2499	33	6958	4.7	2000–2499
33	59	6235	9.5	3000–3499	49	18,791	2.6	2000–2499
34	183	31,390	5.8	3000–3499	18	10,618	1.7	2500–2999
35	306	96,686	3.2	3000–3499	43	30,553	1.4	2500–2999
36	535	324,911	1.6	3000–3499	73	59,748	1.2	2500–2999

The category with the lowest mortality rate was selected at each week, separately for singletons and twins. Each row describes the 500-g birth weight category identified as the optimal birth weight at that specific week, for singletons and twins, respectively. Variations in sample size across weeks of gestation are due to the size of the cell identified as the optimal birth weight category.

[a]Neonatal deaths per 1000 live births.

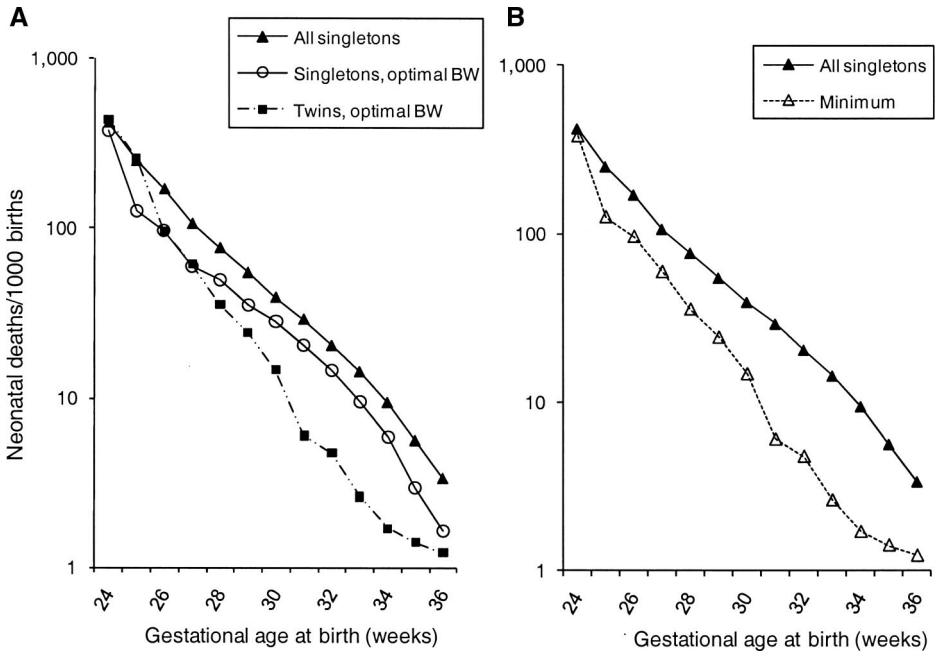

FIGURE 5. A, Gestational-age-specific neonatal mortality for singletons and twins at the optimal birth weight (BW) and (B) synthetic set of rates representing the lowest mortality at each week between singletons and twins. The mortality for all singletons is reported for comparison purposes. Data from National Center for Health Statistics, US Live Births, 1995–2002.

TABLE 2. Observed and Expected Deaths Among Singletons Born Between 24 and 36 Weeks

Week of Gestation	No. Births	Observed Death Rate[a]	Expected Death Rate[a]	(Expected/ Observed) × 100
24	25,575	417.6	378.0	91
25	26,848	248.2	125.5	51
26	30,622	169.1	95.9	57
27	31,993	105.0	59.5	57
28	37,912	75.0	35.6	47
29	42,686	53.9	24.2	45
30	55,877	41.0	14.7	36
31	72,276	29.2	6.0	20
32	107,450	20.7	4.7	23
33	156,886	14.6	2.6	18
34	286,487	9.6	1.7	18
35	535,608	5.7	1.4	25
36	1,095,092	3.4	1.2	36
Total	2,505,312	19.7	10.0	51

Expected death rates are based on the lower of the 2 "minimum" rates shown in Table 1.

[a]Neonatal deaths per 1000 live births.

pathology may itself delay fetal development. Even so, it is useful to consider the effect that immaturity alone would have on an otherwise healthy baby.

As a crude estimate of what might be observed if babies could be randomized to delivery across the preterm period, we have attempted to estimate the mortality due to immaturity by selecting categories of preterm births that we assumed to be relatively less likely to be affected by pathologic conditions. For example, preterm babies born at optimal weights are those least likely to have suffered disruptions in fetal growth.[23,25]

The estimated proportion of mortality due to immaturity alone was lowest (and the proportion due to unmeasured pathology highest) when we included twins. Our rationale for using twins is analogous to previous explanations for the lower mortality of babies of smokers at some low birth weights[15,23,26]—namely that other causes of low birth weight are more lethal than smoking and, given a low birth weight, it is more likely that such a condition is present among the nonsmokers. (We recently demonstrated this explicitly using a model that assumed babies of smokers as having a higher risk at all weights.[23] The empirical evidence supports the same interpretation for twins.[1,14]) When we selected the mortality rates of twins at their gestational-age-specific optimum birth weight, we estimated that the proportion of mortality due to immaturity was half of all preterm mortality. This leaves the other half as due to unmeasured pathology (either alone or interacting with immaturity).

Our analysis has a number of limitations. First, we made simplistic assumptions when selecting groups of preterm babies for study. It is likely that the preterm babies whom we selected as "relatively healthier" nonetheless harbored pathologies that contributed to their preterm delivery and increased their mortality risk beyond that of immaturity alone. To the extent this is true, the actual proportion of mortality due to immaturity alone would be even lower than our estimate. It is also possible that the survival of the babies in this analysis was improved by the administration of prenatal corticosteroids.

Second, our estimates are time- and place-specific. Different estimates would presumably emerge in settings with a

different ability to care for preterm babies, even if our estimates did not suffer from any other problem. Third, the relatively poor quality of gestational age estimates may have affected the selection of babies born at the optimal birth weight. Although we attempted to remove the most obvious errors, we cannot rule out the possibility that the gestational age for the selected babies was higher than the nominal gestational age (and that those infants were thus more mature). Furthermore, the residual effect of gestational age within 1-week intervals may have skewed the selection of babies at the optimal birth weight (ie, the babies with the optimal birth weight might also have been born in the later part of the week). Both misclassified births and those reflecting a higher gestational age within 1 week would, however, tend to be the heaviest in a given gestational-age stratum. In fact, optimal birth weight was often the second- or third-heaviest category (Fig. 4). Furthermore, the quality of gestational age based on LMP appeared to be better for multiples than in singletons (eAppendix [http://links.lww.com/EDE/A387]), perhaps because many multiples are born as a result of infertility treatment and they are the target of more intensive prenatal care. Twins were the basis for 10 of the 13 minimum estimates based on optimal weight.

Our method of "correcting" gestational age is similar to what has been done by others,[27,28] with the difference being that we made use of external estimates of standard deviations[18] to assess whether birth weight fell within specified limits at any given gestation. Among babies classified as preterm by LMP, we excluded 2.4% and reclassified (mostly upward) 29% (eAppendix [http://links.lww.com/EDE/A387]). The method was inherently tolerant of 1- and 2-week errors, but sensitive to larger ones. Although the excluded and reclassified births are not a random sample of all births,[29,30] the birth-weight distributions and birth-weight-specific mortality patterns observed before and after correction (eFigs. 1 and 2 [http://links.lww.com/EDE/A387]) suggest that we excluded or reclassified births that were truly not preterm, thus overall improving the quality of our estimates.

It could be argued that twinning induces stress and thereby accelerates fetal maturation–and that this would in turn explain the lower preterm mortality of twins. Although "stress" in utero appears to result in accelerated lung maturation,[31–34] this does not necessarily translate into improved postnatal respiratory function.[32] Even if twins had a survival advantage due to stress, our assumptions would hold as long as this advantage does not exceed the underlying disadvantage associated with being a twin. Furthermore, babies at the optimal birth weight would likely be among the least stressed of those born at the same week. When we excluded babies born to mothers with a report of placental abruption or incompetent cervix, we saw virtually no change in our results.

Our estimates provide, to the best of our knowledge, the first attempt to estimate preterm mortality due to immaturity alone. The simultaneous presence of different components of preterm mortality helps to explain what have been regarded as paradoxical patterns of gestational-age-specific mortality. Twins and triplets (compared with singletons), babies of preeclamptic pregnancies (compared with other babies), and African-American babies (compared with white babies) have lower mortality at most preterm weeks, even though their mortality is higher overall.[14,35–37] The presence of diverse causes of preterm birth provides an explanation for these patterns of mortality,[1,7] analogous to the argument made for intersecting weight-specific mortality curves.[23]

What are the implications of these estimates? One is that a delay in delivery may not benefit a given infant—and could even increase risk: if preterm delivery is triggered by the presence of an underlying pathology (such as infection), the postponement of delivery will not address the underlying condition, and may cause it to become more severe. A proper evaluation of interventions to delay preterm labor should focus on measures of fetal and infant survival rather than simply on the efficacy of strategies to prolong pregnancy.[13] Similarly, early delivery is not necessarily bad for the newborn. Obstetric intervention in preeclamptic pregnancies in recent years has resulted in earlier births over time, with little change in newborn mortality (and a substantial reduction in stillbirth).[37] This suggests a situation in which a hostile uterine environment is worse than early birth.

Our estimates of the components of preterm mortality are bound to be incorrect. One reason is that they are derived from twins (who presumably have an inherently higher mortality). Another is that we attempted to remove only the direct effect of pathology on mortality, without considering the contribution of pathologies to preterm birth itself. In fact, it is unlikely that the groups we selected are true representations of the healthy immature infant, as these groups are almost certainly contaminated by pathology. This is especially true at the earliest gestations, when virtually all deliveries would presumably be the result of some pathologic process (unless the pathologic process itself contributes to accelerated maturation[38]). Even so, we believe our results are valid in their broad outline and, likely, a conservative estimate. As a rough approximation, it seems reasonable to conclude that at least half of the mortality observed among singleton preterm infants is not due to immaturity alone, but instead reflects the damage done to the fetus by whatever pathologic processes triggered its preterm birth.

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