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A NOTE ON THE FETAL–INFANT MORTALITY PROBLEM

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Summary. This paper considers the age pattern of mortality between conception and first birthday. It highlights the various problems that still limit our understanding of the ways in which the age components of mortality are associated, especially during the perinatal period. A mathematical function is fitted which captures the interaction between six mortality components for a typical high mortality society, one in which the infant mortality rate is 150 per thousand live births. This experiment helps to clarify the need to link infant with fetal mortality, to conduct further research on the level of risk in each component, and to consider the cumulative early-age mortality profile in its entirety.

Introduction

There already exists a voluminous literature on the changing relationship between mortality and age, but the actuaries and demographers find that there are still some areas of uncertainty (Heligman & Pollard, 1980). In recent years attention has focused on the rectangularization of the mortality curve and attempts to estimate the mean maximum length of life (life expectancy at birth, e_0, tending towards 92 years, perhaps). That is, there has been a particular interest in mortality at older ages and especially the financial and social issues surrounding the substantial increase in e_{60} in the Western world. These are, of course, important matters, but there are others of equal significance concerned with the opposite end of the mortality curve. For example, the 'Barker hypothesis' (Barker, 1994) has attracted considerable interest. How does the fetal environment – the experiences of very early age – affect survival chances later in life? Are larger, longer, full-term babies more likely to avoid heart disease in middle age? Quite possibly, premature births face growth problems that have a long-term impact on the likelihood of disability and development in general (Reed & Stanley, 1977). Demographers working on relatively high mortality developing country populations have also become concerned with the associations between the various key segments in the mortality curve and the way they reflect distinctive epidemiological patterns. For example, the associations between infant and early childhood mortality or neonatal and postneonatal mortality have proved

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especially intriguing. In the case of the former, it is clear that in some populations the early childhood mortality rate can be in excess of the infant mortality rate, although it is often uncertain whether this is due to especially high levels of the childhood infectious diseases (measles in particular) or because infant mortality has been systematically underestimated.

Among historical demographers there has been particular concern over the way in which the relationship between neonatal and postneonatal mortality rates change as the overall level of infant mortality declines. Until recently it has also been assumed, following the pioneering work of Jean Bourgeois-Pichat in the early 1950s, that relatively simple biometric techniques could be used to infer the level of endogenous fetal and birth-related mortality from a curve fitted to its age pattern between 28 and 365 days after birth, that is from mortality during the postneonatal period (Galley & Woods, 1999). While this procedure is becoming less popular, the practice of deriving one segment of the mortality curve from another adjacent segment still persists. Most recently there have been attempts to use endogenous (or 0–6 day) mortality to approximate the stillbirth rate (Hart, 1998; Wrigley, 1998).

In this paper existing evidence is reviewed that allows the description of the characteristic shape of the mortality curve between conception and age one year. In addition, the key age segments of the curve are identified, establishing a framework from which to explore the inter-relationship between mortality levels amongst the various segments. Finally, a mathematical model that captures the main features of the birth to first-birthday mortality curve and describes its key features is outlined. In subsequent research this mathematical model is intended to be used in conjunction with the proposed framework of key age segments to address the question: what is likely to happen to the shape of the fetal–infant mortality curve as the background level of mortality changes, for example as the infant mortality rate declines from 150 to 100 to 50 to 10 per 1000 live births?

Characteristic shape

First the variables must be defined. Age has been measured in a variety of ways: days, weeks, months post-fertilization–conception or after last menstrual period (LMP). Although the main concern is with the way in which survival chances vary after conception, it is more convenient to use LMP as a reference device since many of the medical or demographic studies referred to in this study also use this standard. Age is therefore measured in days after LMP with conception at 14 days, clinical pregnancy recognition possible at about 35 days, full-term at 280 days (40 weeks LMP) and first birthday at 644 days (52 weeks after live birth). Mortality risk is measured by considering the number of deaths that have occurred by age x out of 1000 conceptions (in life table terms, where x is given in days, then l_{14} is 1000 and mortality is shown by ${}_{x}d_{14}$ with ${}_{644}d_{14}$ as the maximum). Initially, it will also be assumed that between 14 and 280 days a fetus may be either alive or dead and that between 280 and 644 days an infant may be either alive or dead, that is all live births occur at full-term (Kline, Stein & Susser, 1989; Boklage, 1990; Wood, 1994).

It is a relatively simple matter to define the shape of the typical mortality curve during the first year after birth, as a wide variety of statistical datasets are available

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Table 1. Example fetal–infant life table

Age in days after birth	l_x	Age in days after conception	Age in days after LMP	l_x
		0	14	1000
		7	21	728
		21	35	568
		28	42	532
		84	98	525
		182	196	523
		210	224	520
		238	252	510
0	1000	266	280	500
1	990	267	281	495
7	976	273	287	488
28	958	294	308	479
91	930	357	371	465
182	898	448	462	449
364	850	630	644	425

Note: the infant mortality rate is 150; the perinatal mortality rate, 70; neonatal mortality rate, 42; postneonatal mortality, 108; and the stillbirth rate, 44 (all in parts per 1000).

that cover this period (Woods, 2000: pp. 257–261). One example is given in life table form in Table 1. Here the infant mortality rate ($_1q_0$ per 1000, IMR) is set at 150, a high level but one that was common in nineteenth century England and Wales and which is broadly representative of pre-industrial Western societies before the mortality transition (Woods, 1993; Woods & Shelton, 1997).

Table 1 also shows what is believed to be the pattern of survival in the period between conception and birth that is consistent with such an IMR. Not surprisingly, it is difficult to judge precisely the normal rate of embryo loss in the early post-conception phase because fertilization has to be timed from the last menstrual period and only chemical detection is possible prior to clinical recognition. As Kline *et al.* (1989) point out in their comprehensive review of the available literature, most studies rely either on small samples of normally fertile women or groups experiencing low fecundity and who have joined IVF programmes. The work they summarize does tend to show a distinctive break of slope at roughly 42 days. Although agreeing with the timing of the break of slope, Boklage (1990, p. 1) argues that out of 1000 conceptions only about 250 are likely to reach full-term, and 'that at least 73% of natural single conceptions have no real chance of surviving 6 weeks of gestation'. In contrast, Wood (1994, p. 257) reports studies that give from 660 to 760 conceptions surviving to full-term. There is therefore some room for debate over whether the fetal mortality ratio should be set at 1·3:1, 1·5:1, 2:1 or 4:1 (conceptions:live births) or at some other level. This study follows Kline *et al.* (1989, p. 68) in assuming that 1000 conceptions will produce only 500 live births, and Boklage (1990) in the view that

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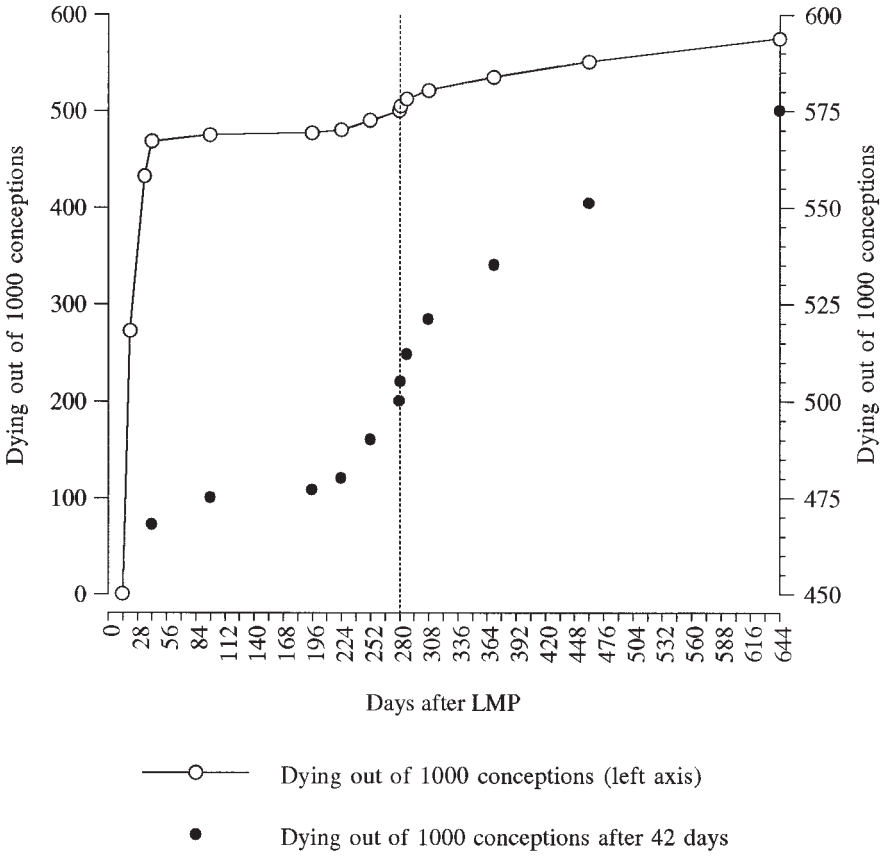


Fig. 1. Fetal–infant mortality curves.

early fetal mortality may follow a double-exponential curve with a break of slope at or about 42 days.

Figure 1 illustrates the cumulative mortality curves consistent with the fetal–infant life table in Table 1. One is shown in its entirety and captures the heavy loss experienced in the days following conception while the second (right axis) focuses on the post-42-day period and highlights the way in which survival chances vary immediately before and after parturition. Figure 1 also helps to illustrate a further complication that must be considered.

It was assumed, initially at least, that a live birth can only occur at full-term, that is at 280 days or 40 weeks, but many babies are born prematurely and in high mortality societies their survival chances are small. Bakketeig, Seigel & Sternthal (1978) provide one of the few detailed studies of fetal–infant mortality for a sufficiently large population to consider the risks at gestational ages from 20 to 46 weeks (LMP) and survival chances up to one year of age. Norway during this period had an IMR of only 12 with a stillbirth rate of 10, but for those born live at 40 weeks

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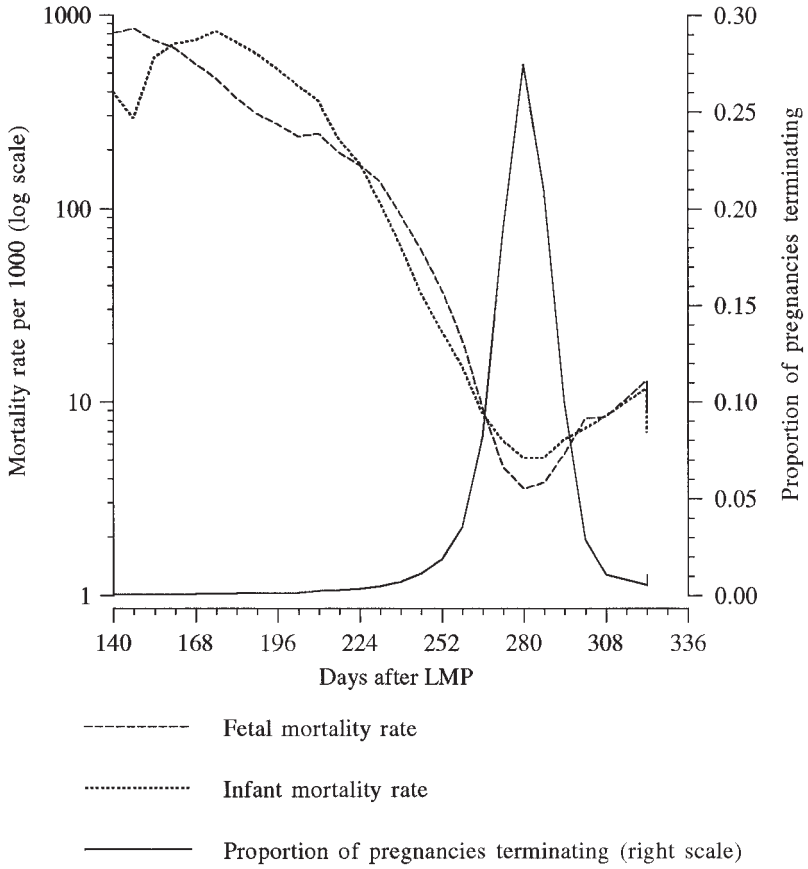


Fig. 2. Fetal and infant mortality rates by duration of pregnancy, Norway, 1967–73. Source: Bakketeig *et al.* (1978).

the IMR was 5. The data analysed by Bakketeig *et al.*, presented in Fig. 2, distinguish between fetal and infant mortality as well as illustrating the clustering of deliveries around full-term. These data suggest an asymmetric s-shape for the fetal–infant mortality curve in the period immediately preceding and following full-term, with a point of inflection centred on full-term. In constructing the data for Table 1 and Fig. 1, the results from Bakketeig *et al.* (1978) have been scaled to correspond with a high mortality regime, although it is fully acknowledged that doing so begs several questions, to be addressed in future research, concerning the degree to which the Norwegian pattern might be replicated in societies with far higher levels of mortality. For example, in Norway (1967–73), of those pregnancies (0·56%) that terminated between 20 and 27 weeks gestation (LMP), 53% ended in a fetal death; the next 32% died in infancy, most during the first day, but the remaining 15% (364 in total) survived to reach their first birthday. It is difficult to believe that these percentages would also apply to a population in which IMR was 120 and not 12. Even so, there

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Table 2. Definition of distinctive segments in the fetal–infant mortality curve

Label	Days after LMP	Name	Deaths out of 1000 conceptions	Proportion of deaths
a	14–41	Embryo	468	0·8139
b	42–195	Early fetal	9	0·0157
c	196–279	Late fetal (stillbirths)	23	0·0400
d	280–286	Early neonatal	12	0·0209
e	287–307	Late neonatal	9	0·0157
f	308–644	Postneonatal	54	0·0938

Note: based on the example in Table 1 and illustrated by Fig. 3.

is no reason to dispute the available evidence presented by Bakketeig *et al.* concerning the fundamental shape of the late fetal and early neonatal curve.

From what can be seen in Fig. 1, and from the judgement of existing studies, it would seem reasonable to divide the fetal–infant mortality curve into six segments between which there are five more or less distinctive turning points. These segments are defined in Table 2 and illustrated in Fig. 3. Table 2 also establishes the relative importance of each of the segments, again using the high mortality example (IMR is 150) shown in Table 1. It is suggested that this will provide a useful framework for investigating and linking the key stages of progress in mortality along the path of conception to first birthday.

A model of fetal–infant mortality

In addition to offering a conceptual framework for investigating fetal–infant mortality, the aim was to establish an empirically based mathematical model that links together the elements of the curve presented in Fig. 3. This follows the path first trodden by demographers such as Bourgeois-Pichat in the 1940s and 1950s (Galley & Woods, 1999). The following is the authors' proposed model of fetal–infant loss from the point of conception to the end of the first year of life, fitted to the illustrative pre-mortality transition data presented in Table 1.

$$\hat{y} = y_0 + Ae^{-Bx} + \frac{C}{\left(1 + e^{\frac{-(x-x_0)}{D}}\right)^E} + \frac{F}{\left(1 + e^{\frac{-(x)}{G}}\right)^H},$$

where $\hat{y}$=predicted fetal–infant loss per 1000 conceptions; x=days after LMP; y_0=473·3523; x_0=280; A= − 2549·0207; B=0·1197; C=28·9374; D=6·8747; E=1·1418; F=84·4912; G=154·7187; H=11·1787.

The model curve comprises four terms and ten parameters. As in any compound curve these terms and parameters interact with one another. However, the model may conveniently be conceptualized as comprising three main components and six

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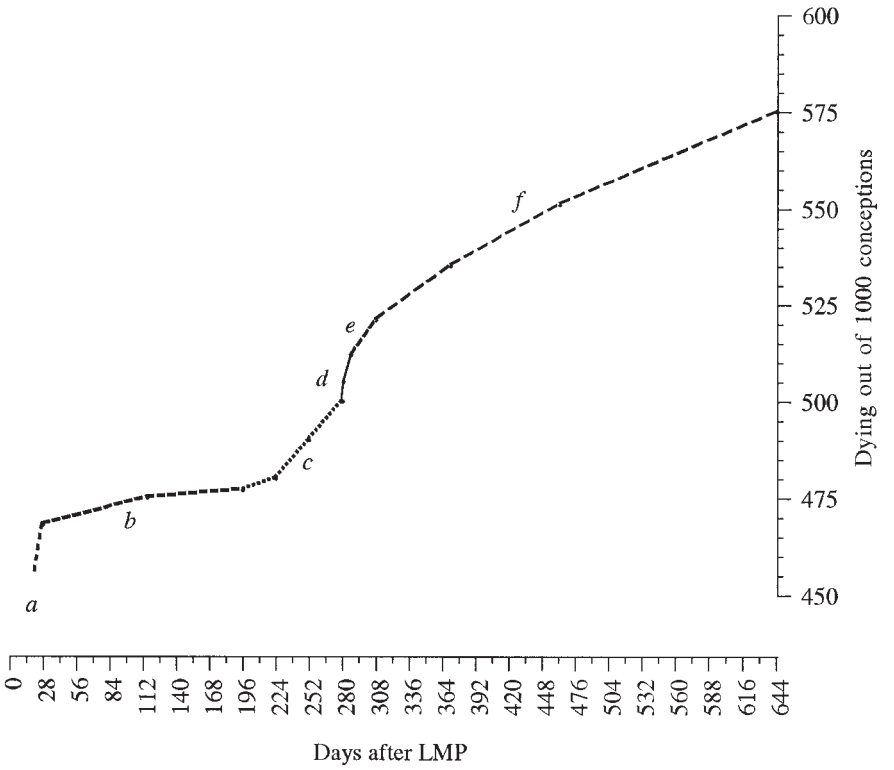


Fig. 3. The six segments of the fetal–infant mortality curve.

segments. The segments have been shown in Fig. 3. Figure 4 illustrates the model curve and its constituent components. An interpretation of the three components and their parameters follows.

Component 1 (segments a *and* b*): embryonic and early fetal loss (14–196 days LMP)*

$$\hat{y}_1 = y_0 + Ae^{-Bx}$$

This is an exponential growth curve with two parameters, A and B, plus a constant term, y_0. Component 1 captures the high mortality portion of the curve associated with embryonic loss (14–41 days LMP), but also contributes to the part of the curve dealing with early fetal loss (42–195 days LMP). The higher the level of B, the more rapidly the death rate increases to a maximum. The higher the value of A, the greater the vertical extent of the rise. The constant term, y_0, offsets the curve vertically by an amount approximately equivalent to the maximum early fetal mortality. The problem of slightly under-shooting embryonic losses at 42 days LMP is not resolved by adopting a double-exponential curve of the form recommended by Bocklage (1990).

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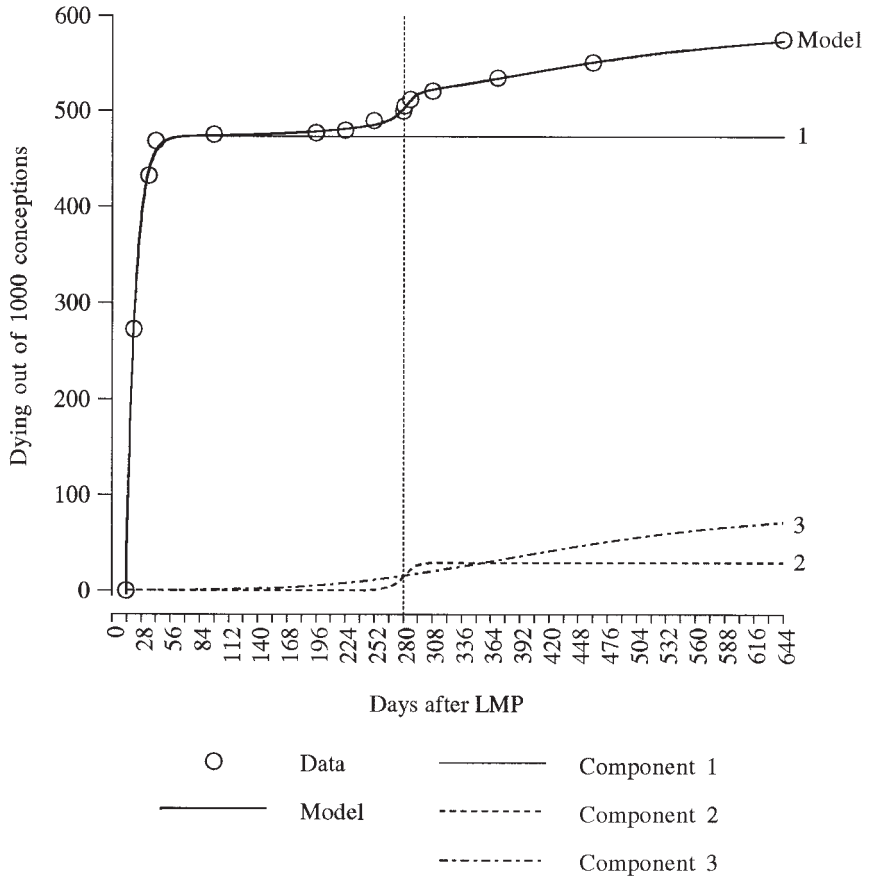


Fig. 4. Model fetal–infant mortality curves.

Component 2 (segments c, d *and* e*): late fetal and neonatal mortality (196–308 days LMP)*

$$\hat{y}_2 = \frac{C}{\left(1 + e^{\frac{-(x - x_0)}{D}}\right)^E}$$

This is an asymmetrical sigmoidal (s-shaped) curve with four parameters: *C, D, E* and x_0. When initially fitted to the residual of the observed mortality data less the embryonic and early fetal loss modelled by component 1, the parameters of the curve have the following interpretation. *C* equals the difference in mortality between the start and the end of the curve (i.e. the difference in mortality between the start of the late fetal period and the end of the neonatal period). *D* controls the gradient of the slope, with higher values of *D* yielding gentler inclines. *E* controls the asymmetry of the slope and must take a value >0. A value of 1 produces a symmetrical curve, with the point of inflection half-way between the lower and upper mortality bounds

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of the curve. Values of $E<1$ raise the inflection point giving rise to gentler 'entry' and steeper 'exit'. Values of $E>1$ lower the inflection point giving rise to a steeper 'entry' and gentler 'exit'. Late fetal mortality is modelled by the part of the curve to the left of the inflection point, neonatal mortality by the part of the curve to the right (x_0 is the empirically defined inflection point of the curve at 'full-term' in terms of days since LMP). When combined with component 3 some of the direct interpretation of these parameters is lost. For example, C is no longer exactly equivalent to the difference in mortality between the start and the end of the late fetal period. However, the general interpretation still applies. For two curves with differing values of C, the one with the higher value is likely to be the one with the higher level of late fetal loss. Similarly, lower values of D would indicate steeper curves, and differing values of E would indicate greater or lesser asymmetry across the late fetal and neonatal periods.

Component 3 (segment f*): postneonatal mortality (308–644 days LMP)*

$$\hat{y}_3 = \frac{F}{\left(1 + e^{\frac{-(x)}{G}}\right)^H}$$

This is another asymmetrical sigmoidal curve, but with only three parameters: F, G and H (no x_0). The primary purpose of this term is to model postneonatal mortality. In this context the parameters F, G and H may be interpreted as follows. F reflects the difference in mortality between the start and end of the postneonatal period. Unlike C, F does not directly measure this difference because at 644 days LMP the curve has yet to level out. G controls the gradient of the curve in a manner similar to D for component 2. H controls the asymmetry of the curve in a manner similar to E for component 2. The values of G and H are considerably higher than for D and E, reflecting lower death rates in the postneonatal period.

In this curve the x_0 term found in the equation for component 2 has been omitted (set to 0). By experimentation it has been found that either this term or the parameter H can be omitted without harm to overall model fit. Omitting an x_0 term from component 3 is preferred. This helps to ensure that the modelled inflection point between the late fetal and neonatal periods remains a close approximation to the empirically observed value (x_0 in component 2).

Although the main purpose of component 3 is the modelling of postneonatal mortality, its interaction with the other two components helps to significantly improve model fit at the margins. In particular, the interaction of component 3 with component 1 ensures a very slowly increasing rate of loss during the early and late fetal periods. On its own the exponential curve of component 1 models this period as one of a very slowly decreasing rate of loss, the curve being almost linear in nature. The interaction of component 3 with component 2 serves to reinforce the asymmetry of the curve across the early and late neonatal periods. Conversely, the interaction of component 2 with component 3 ensures that the postneonatal period is modelled as a rising curve. Without the interaction between components 2 and 3 this period would be modelled by component 3 as one of an initially increasing rather than decreasing mortality risk.

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For those readers interested in exploring the complex interactions of the various model components and parameter further, details on how to obtain a computerized version of the model are given in the Appendix.

Model fitting

At present, data on prenatal and in particular embryonic and early fetal losses are slight. To fit satisfactorily this model to the data in Table 1 it has been necessary to interpolate points between those already known. Unfortunately, the parameters produced by curve-fitting can vary significantly depending upon the precise points fitted. For example, it has been found that the first segment of the curve is best fitted using only a few points (to ensure that the loss at 14 days after LMP=0), while the second segment can only be fitted after extensive interpolation. In consequence, the precise fit of the model curve depends upon the interpolated values used. However, as a guide, the fit of the model specified above to the data presented in Table 1 has an r^2 of 99·9%. Further technical information about the curve-fitting process may be found in the Appendix.

The model curve and its fit to the data in Table 1 are shown in Fig. 4. Overall, the fit of the model to the known data on fetal–infant loss appears very close. On closer examination, three areas of weakness may be detected. First, as the curve levels out from its initial steep rise, it slightly undershoots the maximum recorded embryonic loss at 42 days LMP. Second, the general shape of the asymmetric neonatal loss curve is captured, but the fit to the known data is not exact. Third, the model slightly undershoots the final infant mortality rate. The extent to which these are real problems, rather than symptoms of the rather speculative nature of some of the data being fitted, is difficult to determine. In any case the third problem could probably be corrected by fitting the model to a time series that stretched into at least the early days of the second year of life.

Discussion

The authors' proposed conceptual and mathematical models of the fetal–infant mortality curve have, they believe, made the following advances possible. First, they have helped to refocus attention on the fetal–infant mortality problem and the many empirical uncertainties that still surround attempts to measure accurately the pattern of survival at very early age. Second, they have suggested a way in which the interests of medical statisticians, demographers and epidemiologists may be combined to enhance our understanding of the critical periods for human fertility, namely those immediately following conception and just prior to parturition (Leridon, 1977). Third, they provide the basis for further work on the links between the six segments (three components) and the ways in which they may vary as the level of, say, infant mortality changes. For example, should the conception:live birth ratio be expected to fall as infant mortality declines, or are the two largely independent of one another? In terms of perinatal mortality, should its two elements (stillbirths and deaths during the first seven days after live birth) be expected to be so tightly connected that the one

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may be used to estimate the other? How may the role of prematurity and its variable influence on infant mortality be incorporated? The models outlined in this paper will assist the addressing of these and other related questions.

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Appendix

Parameterization of the fetal–infant mortality model

For a computerized version of the mathematical fetal–infant mortality model presented in this paper (currently spreadsheet-based), please visit the project website: http://pcwww.liv.ac.uk/~william/fetal-infant/

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The model allows interested readers to explore more fully the interactions between model components and individual parameter values.

The parameter values for the fitted model were obtained using the curve-fitting routine in SigmaPlot (SPSS Inc.), which uses the Marquardt–Levenberg algorithm to minimize the sum of the squared differences between observed and predicted values. The data used for fitting purposes comprised the data presented in Table 1 plus additional points added by visual interpolation. Copies of the original and interpolated datasets may be obtained from the project website, as may full details of the model-fitting procedure.

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