

EDITORIAL

The implications of late-preterm birth for global child survival

David Osrin

UCL Centre for International Health and Development, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

E-mail: d.osrin@ich.ucl.ac.uk

Risks associated with late-preterm birth

The article by Gouyon *et al.*¹ in this issue adds to a limited collection on the health of late-preterm infants. Using a population-based dataset of over 150 000 singletons born alive at 34–41 weeks gestation in Burgundy in 2000–08, the authors showed a serial reduction with gestational age in the risk of death or severe neurological condition, from an adjusted relative risk of 6.8 [95% confidence interval (CI) 4.1–11.1] at 34 weeks to a comparative nadir at 39–41 weeks. There was a reduction in respiratory disorders requiring oxygen and either continuous or intermittent positive airway pressure support, from a relative risk of 61.0 (95% CI 54.1–86.9) at 34 weeks. They also found higher risks for infants born at 37 and 38 weeks than for later term infants, suggesting that our view of term as running from 37 to 41 weeks could be more nuanced. The findings are broadly similar to those of Shapiro-Mendoza *et al.*², who used US certification data to compare 26 170 late-preterm with 377 638 term infants. The risk of morbidity doubled for each week of birth earlier than 38 weeks, with a relative risk of 20.6 (95% CI 19.7–21.6) for infants born at 34 weeks. A population-based Canadian study of 88 867 live-born infants showed a relative risk of respiratory morbidity of 4.4 (95% CI 4.2–4.6) and of infection of 5.2 (95% CI 4.6–5.9) in late-preterm compared with term infants.³

Preterm infants born in the later weeks of pregnancy are a relatively under-researched group.⁴ Preterm labour is generally no coincidence, and infants born early differ systematically from those born at term. The maternal morbidities documented by Gouyon *et al.*¹ attest to this (24% of mothers of infants born at 34 weeks had two or more defined antenatal complications, compared with 2% of mothers of infants born at 39–41 weeks), as does the fact that 17% of 34-week infants were small for

gestational age; by definition, 10% should be. Additionally, the increased risk is not explained by congenital abnormalities.^{5,6} In 2007, Engle *et al.*⁷ proposed that we move towards an explicit acknowledgment of the potential problems, defining late-preterm as from 34^{0/7} to 36^{6/7} weeks after the beginning of a mother's last menstrual period (or 239–259 days inclusive). Late preterm infants are more likely to experience illness than term infants, particularly as a result of thermal instability, hypoglycaemia, respiratory distress, apnoea, jaundice and feeding difficulties.⁴

Implications for morbidity, mortality and health care

There has been a tendency to see the morbidity associated with late-preterm birth as relatively manageable and unlikely to have substantial population effects on mortality and long-term morbidity, but this view is optimistic. US figures suggest that late-preterm accounted for 74% of all preterm in 2002,⁸ and the proportion is rising.⁹ In population terms, Kramer *et al.*⁵ showed that preterm infants born at 34–36 weeks gestation comprised ~7% of live births in a 1995 US cohort and ~5% in a 1992–94 Canadian one. These figures imply a substantial need for care.¹⁰ McIntire *et al.*¹¹ analysed records of about 250 000 live-born singletons between 34 and 40 weeks gestation over 18 years in a Texas hospital, and found that late-preterm infants made up 76% of preterm infants and 9% of the cohort. Three per cent of infants born at 34 weeks required ventilation, 5% needed intensive care and 31% were investigated for sepsis. Shapiro-Mendoza *et al.*² described morbidity in 22% of late-preterm infants and in 52% of infants born at 34 weeks. There is a range of projections of the need for intensive care, with some authors suggesting that as many as 50% of infants born at 34

weeks require it.¹² Gouyon *et al.*¹ describe admission to a neonatal unit for 97% of infants born at 34 weeks, but this is likely to depend on the threshold for admission and the level of neonatal care required.

Even in high-income countries with strong health-care systems, late-preterm morbidity does lead to loss of life. Khashu *et al.*³ described a 5.5-fold increase in neonatal mortality (95% CI 3.4–8.9) in 33–36-week preterm infants compared with term infants, and the relative risks of early neonatal death (in the first 7 days) in the US and Canadian cohorts described by Kramer *et al.*⁵ were 5.2 (95% CI 4.8–5.6) and 7.9 (95% CI 6.7–9.2), respectively. Perhaps more tellingly, the late preterm groups contributed aetiological fractions of 6.3 and 9.0% to early neonatal deaths in the two cohorts, and 13.1 and 15.9% to neonatal deaths (in the first 28 days).

Late-preterm—and even early-term—infants are, then, at increased risk of morbidity and mortality. The data that show this come from high-income countries in North America and Western Europe, with strong health-care systems and recording processes at hospital and population level. There are, however, broader implications. Of an estimated 3.8 million annual neonatal deaths,¹³ 98% occur in low- and middle-income countries.¹⁴ Neonatal mortality currently makes up >40% of global under-5 mortality,¹³ and this proportion has risen as post-neonatal deaths have fallen, largely because of fewer deaths from acute respiratory infection, diarrhoea and vaccine-preventable diseases such as measles. Our understanding of the causes of neonatal death is limited by the fact that greater need accompanies weaker documentation. About 65% of births in South Asia and East and southern Africa take place at home,¹⁵ and estimates of cause-specific mortality rely on models and approaches such as verbal autopsy. The three commonest causes of neonatal death are complications of prematurity (30%), infection (28%) and intrapartum-related ('birth asphyxia') (24%).¹³ These broad-brush estimates are for single causes, and there is likely to be crossover co-morbidity. For example, both preterm delivery and presumptive asphyxia are associated with infection. It also seems reasonable to suggest that sequelae of late-preterm might be classified under other headings, particularly if the associated morbidity has been underestimated.

The global issue of low birth weight

The 20 million low birth weight infants born annually, 72% of them in Asia, have an increased risk of mortality. They constitute a variable segment of the newborn population, from 7% in high-income to 19% in least developed countries (and 27% in

south-central Asia).¹⁶ Defined as a birth weight of <2500 g, low birth weight is a crude indicator that includes infants who are preterm, infants who are term but small and infants who are both preterm and small for gestational age. Belizan and Villar first pointed out that, the higher a country's proportion of low birth weight infants, the more of them are born at term.^{17,18} A (reasonable) assumption is that this group of term low birth weight infants have suffered intrauterine growth restriction, and that much of this might be explained by nutritional insufficiency in their mothers. If most low birth weight infants are growth restricted but mature, and if low birth weight is on the causal pathway to neonatal mortality—runs the argument—then what we need to do is improve fetal growth. The flaw in this argument is that it assumes that the mortality contributed by the term group of infants is substantial, and that birth weight is sufficiently causal to yield mortality reductions if tackled. This flaw may not seem important, particularly since the alternative—preventing preterm delivery—has been an elusive goal in even the most sophisticated clinical settings. Bound up as it is with issues of women's health, child health after the neonatal period, and the right to adequate nutrition, it would be inappropriate to argue against improving fetal growth prospects in poor populations. Healthier women with access to nutritious foods have healthier, larger babies with a higher chance of survival.

There are two problems, however. The first is that we do not yet understand enough about the longer term effects of changes in fetal growth trajectory. The second is that the sequence of reasoning discussed above might lead to disappointment if our efforts to improve fetal growth do not lead to major reductions in neonatal mortality. Both of these problems have recently arisen.

The relationship between the weight of an infant and her survival is not straightforward. Wilcox argued that the distribution of birth weight follows a negatively skewed bell curve, the skew accounted for by a residual distribution of (generally) preterm infants superimposed on a predominant distribution of (generally) term infants.¹⁹ The idea is that weight itself is a limited descriptor of mortality, and that different groups (US Hispanic, African-American and White European infants, infants born to mothers who smoke and infants born in populations living at altitude) show similar curves with different means. A low birth weight US Hispanic infant has, on population average, better survival prospects than a US White European infant of identical weight. This finding fits with the experience of neonatologists, at least with respect to early preterm infants on intensive-care units, and the same pattern seems to be seen for late-preterm.

Wilcox was accused of supporting biological determinism—unjustly, in my opinion—and it may be some comfort that subsequent work does not falsify his hypothesis. For example, using US National Center for Health Statistics records, Alexander *et al.*⁸ showed higher gestation-specific survival in Black preterm infants, followed by Hispanics and then by Whites. However, the likelihood of being born early followed the same sequence. The 33–36-week infants constituted 12% of live-born Black infants, 8% of Hispanic and 7% of White; and neonatal mortality was higher in term Black infants.⁸ The impression (teleologically, I admit) is of resilience in the face of greater environmental adversity. This has much in common with the emerging body of work on the developmental origins of health and disease, which emphasizes the trade-off between adaptation to the periconceptional, fetal and early infant environment and longer term outcomes such as insulin resistance, lipid metabolism and cardiovascular disease. New ideas about the transgenerational effects of environment, and particularly epigenetic modification, could explain the differences between Wilcox's bell curves. They also raise questions about efforts to intervene. For example, if Indian children born in food insecure conditions are maladapted to future food sufficiency,²⁰ will increased nutrient availability to the growing fetus do good or harm?²¹ This is not simply an academic question, and a great deal of research is underway—from epigenetics to behavioural change—to answer it.²²

The second problem lies with the choice of term intrauterine growth restriction as a lever for preventing neonatal mortality in low birth weight infants in low-income countries. One might see this as the result of limited consideration of population attributable risk, although the statistics on which to base calculations are scanty in the populations at most risk; assignment of gestational age is difficult and population-based studies are few. In an analysis of outcomes for low birth weight infants born at a hospital in Dhaka, Bangladesh, Yasmin *et al.*²³ found that 75% of deaths occurred in the preterm group, although it constituted only 39% of the cohort. With respect to later preterm, infants of 32–36 weeks gestation contributed an aetiological fraction of 55%. This begged the question (already asked by Wilcox) of whether a focus on growth might have only limited effects on survival. Efforts to improve outcomes have had disappointing results, an example being the relative lack of success of public health programmes to prevent low birth weight.²⁴ Another example is the recent experience of trials of antenatal multiple micronutrient supplementation, which is associated with increases in birth weight that do not seem to translate into increased neonatal survival.^{25,26} Although this may be explained by the modest weight increase (macronutrient supplementation

appears to be associated with greater weight increments and some reduction in neonatal mortality),²⁷ it is a sobering finding.

How much of neonatal mortality is attributable to late-preterm?

We can only speculate on the fraction of neonatal mortality attributable to late-preterm in low-income countries. Rates of preterm birth do appear to be higher than in high-income settings (12.3%, for example, in a population-based study from South India),²⁸ but gestation-specific mortality rates are largely unknown. Using records of preterm infants born at a tertiary hospital in Nigeria, Kuti and Owa found essentially zero survival for infants born at gestations of <28 weeks. The data presented in their article suggest a neonatal mortality rate of 370 per 1000 for infants <34 weeks, and 48 for infants 34–36 weeks, an 8-fold difference. What we do not know is how late-preterm morbidity of the degree described by Gouyon *et al.*¹ is reflected in survival rates in populations where clinical support does not reach many newborn infants.

Speculatively, we could estimate aetiologic fraction (EF) using the approach described by Miettinen and others:^{5,29,30}

$$EF = P_i(RR_i - 1) / \sum P_i(RR_i - 1) + 1$$

where P_i is the prevalence of the i -th gestational age category (preterm <34^{0/7}, late-preterm 34^{0/7} to 36^{6/7}), RR_i is the relative risk of mortality in the group compared to the term category, and Σ indicates summation over the i preterm categories. Assuming a relative risk of mortality in late-preterm infants of about 5 (based on a middle figure from the studies already discussed), a relative risk of, say, 20 in infants born before 34^{0/7} and a population proportion of 12% for preterm birth, of which 75% are late-preterm, the estimated EF for late-preterm is ~19%. Varying the relative risk of earlier preterm between 10 and 30 moves the EF between 22 and 16%. If the relative risk of earlier preterm is moved any higher, the combined aetiological fraction for preterm becomes implausibly high. On the other hand, a relative risk of 5 seems conservative given that this is what is observed in hospital settings in high-income countries, and the estimates do not include twins, whose mortality is higher and whose births cluster in the late-preterm category. The imprecision of these estimates notwithstanding, if preterm accounts for at least 30% of neonatal mortality in low-income countries, it seems reasonable to propose that between a third and half of this could be accounted for by late-preterm: between 10 and 15% of global neonatal deaths.

Late-preterm and global neonatal mortality

The article by Gouyon *et al.*¹ should stimulate a little more consideration before late-preterm elective induction of labour or operative delivery in the hospitals of the North. If it makes us think about the toll that late-preterm birth may be taking in the global South, all the better. A recent analysis by Kramer and colleagues raises the question of whether we could profitably turn our attention to managing the consequences of low birth weight rather than preventing it.²⁸ We need to encourage mothers, families and health professionals to think about low-intensity home and hospital interventions that could improve the survival of late-preterm infants. Over the last two decades, newborn survival initiatives have emphasized hygienic delivery, early and exclusive breastfeeding, skin-to-skin contact (late-preterm infants are ideal candidates for Kangaroo mothercare) and early treatment for signs of illness. Our developing understanding of the hazards of late-preterm birth supports this approach unequivocally.

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