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Review

Long-term outcome for the tiniest or most immature babies: survival rates

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SUMMARY

This article focuses on the survival rates of the most immature babies considered viable from around the world. It discusses the various factors in terms of definition, inclusion criteria and policy which can result in marked differences in the apparent rates of delivery (all births), live birth, admission to neonatal intensive care and ultimately survival seen between otherwise similar countries, different regions of the same country, and even adjacent hospitals. Such variation in approach can result in major differences in reported survival and consequentially have large effects on apparent rates of adverse long-term outcome.

1. Introduction

The aim of this edition of *Seminars in Fetal and Neonatal Medicine* is to discuss the long-term outcome of the tiniest and most immature babies. These babies represent the 'cutting edge' of neonatal medicine throughout the developed world, and the appropriateness, or not, of offering active intensive care to these babies is a matter of great debate and polarised views (http://justice4jayden.webs.com/). It is clear that babies who do survive after delivery at 22, 23 or 24 weeks are likely to need at least 4–5 months of inpatient care after birth (sometimes much longer) and are at high risk of death or disability [1,2]. Having a clear understanding of these risks is important for clinicians in counselling parents, and in enabling families to make informed decisions regarding how such babies should be managed. However, published data can be confusing, with apparently very different rates of survival, and these differences inevitably have an effect on reported rates of longer-term adverse outcome as the child grows. In this paper we review the range of influences that can result in both real and artefactual differences in survival and, as a result, affect reported rates of adverse long-term outcome.

2. Defining the cohort: gestation or birth weight?

One of the most important issues when studying extreme preterm birth is the need for a clear definition of the cohort being studied. Including the tiniest (defined by birth weight) and most immature (defined by gestational age) babies inevitably leads to a lack of standardisation of the cohort. Gestational age is a fixed measure at any one point in time, independent of both birth weight and fetal growth (an important factor in studies of the preterm infant), whereas birth weight is biologically dependent upon both gestational age and fetal growth [3]. So a group defined by weight will include a mixture of immature babies and more mature babies with a degree of growth restriction, particularly those from multiple births. Studies of preterm birth indicate that unless a combination of both extreme immaturity and severe growth restriction co-exist then it is the influence of gestation which has the greatest influence on survival [4].

3. Reported survival rates

Mortality rates of the most immature babies have been reviewed previously, identifying significant variation between settings [1,2,5–8]. Reported rates of survival in studies based on geographical or quasi-geographical cohorts have not to date reached double figures at 22 weeks, but at 23, 24 and 25 weeks of gestation reported survival rate has ranged from 0 to 53%, 3 to 70% and from 29 to 85%, respectively. These survival data have been extracted from studies that span over 20 years but few have examined changes in the same population over time. Studies in the UK have identified improved survival for babies at 24 and 25 weeks of gestation between the 1990s and the second half of the first decade of the 21st century. Nevertheless for babies born before 24 weeks of gestation there was little change [9,10]. Studies in Sweden [5,11] are a little more difficult to examine in terms of like-for-like comparison, but again outcome generally improved with time and

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the reported survival rates are substantially higher than in the UK. By contrast, data from Australia for this same group of babies showed no change in survival between 1997 and 2005; however, survival rates in the latter cohort were comparable with contemporaneous European cohorts [12].

4. Scientific advances over time

One of the greatest influences on reported survival rates of the most immature babies is that of changes over time and the definition of 'the tiniest and most immature babies' at different points in the development of neonatal care. This change primarily reflects developments in neonatal care and the view of those providing care about what is feasible at that time (in terms of technology and resources). Some advances such as the availability of exogenous surfactant and the widespread use of antenatal corticosteroids clearly have had a very major influence on what is possible. It may be obvious, but nonetheless worth emphasising, that the perception of 'what is possible' still varies enormously around the world, and for this reason it is easier to consider survival of the most immature babies in the broadly similar settings provided in the developed world.

5. Type of study

In general, rates of survival or long-term outcome are reported either for a geographically defined population (such as births from mothers living in a whole country or a particular region) or a single hospital or group of hospitals where the catchment area is generally less well defined. Population-based studies that report the outcome of all babies alive at the onset of labour (or 'potential live births') can be considered a gold standard. Rates of survival in these studies will generally be lower as they use total births (live births and intrapartum stillbirths) as a denominator. Bt contrast, studies based on hospitals generally have higher survival rates as they tend to use either live births or neonatal unit admissions as their denominator, since the total number of births is usually not known or cannot be calculated (as some babies are transferred into the neonatal unit from elsewhere). The use of these different denominators for calculating survival will strongly influence the rates of reported survival. For example, a hospital reporting the outcome of babies born at 22–24 weeks of gestation will produce very different rates of survival depending on whether the denominator is all births, all those alive at the onset of labour, live births, or neonatal unit admissions at that gestation – the latter will clearly produce the highest reported rate of survival [13]. The inclusion of babies transferred from elsewhere (particularly postnatal transfers) will further influence the results since, in order for the transfer to be possible, the baby will generally have to have been in good condition. Since these different types of study populations vary fundamentally in their make-up, in wider comparisons with other published studies only those that include all births alive at the onset of labour as a denominator can really be used as the basis of reliable comparisons.

Whereas it is generally easy to predict the influence of decisions on which babies to include when reporting mortality among the most immature babies, estimating the influence on neurodevelopmental outcome is far more difficult. Geographical studies minimise selection bias, but, with hospital-based series, the anticipated better survival rates due to the transfer into tertiary centres of those most likely to survive may lead to a larger proportion of infants surviving with long-term disability. Readers should keep these potential influences in mind when reading articles reporting outcomes of this type.

6. Inclusion of terminations

Among the many factors that affect the apparent rates of survival for babies born at the lowest gestation is the issue of whether or not babies born after a termination of pregnancy are included in the denominator and/or the numerator. This is an issue that primarily affects population-based studies, especially comparisons between countries, and is dependent on a variety of legislative differences in respect of under what circumstances and up to what stage of pregnancy termination may be offered. Therefore in comparisons of survival of the most immature babies between countries, it is important to identify whether or not terminations of pregnancy have been included. Those countries where terminations are included in the numerator will have poorer survival rates since inevitably they are all deaths [14].

In the wider context, the approach to termination in a particular country has consequences for other early life outcomes such as increasing neonatal mortality due to congenital anomalies in countries where these are either not detected and/or termination is not offered early in pregnancy. However, this issue affects mainly mature infants.

7. Congenital anomalies

Although generally not an issue for national comparisons, academic studies of very immature babies will often choose to exclude babies with a 'major' congenital anomaly. Fortunately major anomalies are rare among this group and hence they generally have little impact on reported rates of survival. However, in these circumstances different interpretations of what constitutes a major/lethal anomaly (and hence the babies included or excluded) will have an impact on survival.

8. Impact of variation in rates of prematurity

For each of the known influences on reported survival discussed so far, it is possible to have an appreciation of the type of 'bias' introduced – for example, as a result of the study type and exclusion/inclusion criteria. However, the scale of the impact of other influences is much more difficult to estimate.

The March of Dimes regularly publishes data on its website (http://www.marchofdimes.com/peristats/Peristats.aspx) demonstrating marked differences in the rate of very preterm birth between states in the USA. Similar data exist which show wide variations in very preterm birth rates between countries of the EU (Fig. 1) and globally [17]. Whereas these apparent ethnographic differences have a huge influence on the need for neonatal services in these states/countries, there will almost certainly be a parallel effect on the number of babies born at the lowest gestations. There are no data to determine whether this variation translates into differences in how these babies are managed, cared for, or registered, and their subsequent outcomes either in terms of survival or longer-term health status.

It is well established that socio-economic deprivation is a major influence on rates of very preterm delivery. It seems likely that different background rates of deprivation, with their associated exposures and lifestyle influences, are responsible for a significant proportion of the differences seen in the rate of very premature delivery between countries and regions. Interestingly there are data to demonstrate that, in the short term, the neonatal course of children born to mothers from socio-economically deprived areas is no different from that for babies of the same gestation born to mothers from less deprived areas [18]. However, in stark contrast, there is good evidence that the factors that constitute socio-economic deprivation are often associated with poorer neurodevelopmental outcome in childhood.