

Extreme Prematurity Outcomes: Have We Really Reached the Limit?

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Health care professionals and laypeople alike are convinced that outcomes of very preterm infants have been steadily improving over the years. Yet in an interesting article published in this issue of *Pediatrics*, Stensvold et al¹ challenge this belief. In short, the authors conducted an area-based study in Norway in 2013–2014, collecting data on outcomes of all pregnancies ending either in stillbirth or in a live birth from 22 to 26 weeks of gestation. Compared with an analogous study carried out in 1999–2000, they found an increase in the absolute number of such pregnancies, with an increase of intrauterine deaths before admission to the hospital and no improvement thereafter. These results are both surprising and thought-provoking.

This lack of improvement is surprising in view of the great improvements in obstetric and neonatal care in the past decade, including the widespread use of antenatal corticosteroids even at low gestational weeks, improvements in delivery room management and thermoregulation, and improved ventilatory and nutritional strategies. Many studies, both area-based and not,^{2–9} have shown an improvement in mortality and morbidity over the years, so it is necessary to try to understand the reasons for these disappointing results above and beyond the effect of chance and small numbers (a type II error).

A first consideration is that the 2 populations studied in 1999–2000 and 2013–2014 might differ in some important health care determinant. Differences in ethnic, social, and cultural status are among the likely

candidates. As with all other studies with historic controls, we cannot be sure of comparability of populations apart from gestational age.

Even if this was an area-based study, a complete ascertainment of cases does not guarantee against selection bias.¹⁰ In fact, pregnancies were included in this study if they ended in a very narrow window of weeks. If obstetricians/gynecologists have changed attitudes and procedures regarding the management of pregnancies at a gestational age around the “limit of viability” over the past 15 years, then the ability to transform stillbirths at 20 to 21 weeks in 1999–2000 (ie, not contributing data) to deliveries or stillbirths at 22 to 23 weeks (ie, captured in data collection) in 2013–2014 would spuriously increase mortality in the recent cohort. In fact, although the total number of pregnancies in the 2 periods remained the same, those ending at 22 to 24 weeks increased 29%, and it is likely that their features and baseline risk could be different. Moreover, comparing the outcomes at only 22 to 26 weeks is like comparing the outcomes of 2 arms of a clinical trial observing only a small part of the survival curve. Even if the segment 22 to 26 weeks has the same mortality hazard in the 2 surveys, this does not imply that the overall mortality is the same. In fact, it is not the same: the overall neonatal¹¹ and infant¹² mortality rates have both almost halved in Norway between 1999–2000 and 2013–2014, with a steady decline during the years considered.

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Taking into account this complex time-dependent interplay is difficult; in general, analyzing data conditioning on gestational age can be tricky.^{13,14} An approach based on “fetuses at risk” has been proposed to explain changes in obstetric management¹⁵ but is fraught with problems when also studying postnatal outcomes.^{16,17}

Comparability of populations aside, the key question for all obstetricians and neonatologists is what these results mean from a generalizability standpoint relative to other countries or other periods of time. The great strength of this study, its complete area-based coverage, also represents its weakness. Representativeness is necessary for description but is not sufficient for generalizability.¹⁰ Different countries have different data collection systems, especially at low gestational ages,¹⁸ making comparisons difficult. Moreover, different countries have different health care structures.^{19,20} The size of observation areas matters as well. The population of the study (120 007 total births, 251 infants 22 to 26 weeks out of 423 admitted in 9 NICUs in 2 years) represents approximately half of the population in a region of Italy like Lombardy or in other European regions. In these countries, variability between centers and areas is still wide, and Norwegian results could apply to well-defined areas but not to others.

A final lesson that we can draw from this study is that availability of good data are key to objective measurement of strengths and weaknesses of our own perinatal care. Comparing neonatal outcomes across countries represents a great opportunity for quality improvement. To this aim, neonatal networks are well established worldwide,^{3-5,9,19} and there is need for sharing a minimum data set and methodology that could ease feasible and meaningful comparisons. Initiatives are going on to accomplish this goal¹⁹

Maybe somewhere limits have been reached for the current management of extremely preterm infants, but even in highly developed countries, simple evidence-based effective interventions are not always used^{21,22} and represent “missed opportunities” for a better outcome.

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