

# Keeping Up With Outcomes for Infants Born at Extremely Low Gestational Ages

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**Neonatal intensive care** has been one of the success stories of the past 30 years, with steadily improving survival and slowly improving long-term outcomes for infants born early. In the 1980s, few infants born at 25 through 26 weeks of gestation survived, but now high survival and low morbidity rates are expected throughout the developed world. The outcome for infants born at the decreasing limit of viability has continually evoked anxiety in terms of the balance between poor survival with high rates of neuroimpairment and the burden of providing intensive care for many weeks or months. In 1980, this limit was 25 through 26 weeks; now it is 23 weeks. This issue is frequently described as an ethical dilemma as to whether intensive care should be instituted for these children.<sup>1</sup>

One of the major issues that confound attempts to provide hard management guidelines is the continual improvement in mortality, which brings with it changes in attitudes toward survival. Large epidemiologic studies have been performed worldwide, such as EPICure and EPICure 2 in the United Kingdom,<sup>2</sup> a series of reports from Victoria, Australia,<sup>3</sup> the first EPIPAGE (Etude Epidémiologique sur les Petits Ages Gestationnels) study from France,<sup>4</sup> the EPIBEL (Extremely Preterm Infants in Belgium) study from Belgium,<sup>5</sup> and EXPRESS



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(Extremely Preterm Infants in Sweden Study) from Sweden.<sup>6</sup> This issue of *JAMA*

*Pediatrics* contains the headline report from the EPIPAGE-2 iteration, covering births in France in 2011.<sup>7</sup> Such studies are expensive to perform and comprise herculean effort, involving obstetric, neonatal, and eventually developmental medicine in an effort to capture information on all births. These data are then frequently used as a basis for counseling parents and decision making in the perinatal and neonatal period, but equally important they shed light on a range of issues from brain development to service delivery.

The results of EPIPAGE-2 reveal improvement in survival of 14% for 25 through 31 weeks of gestation since 1997 but no appreciable difference in survival at less than 25 weeks. The use of interventions known to improve outcomes (eg, antenatal corticosteroids and surfactants) and other interventions for which evidence is wanting (eg, induction and cesarean section) increased the number of births at 24 weeks and greater. In parallel, the proportions of infants born with major neonatal morbidities (eg, brain injury, necrotizing enterocolitis, and bronchopulmonary dysplasia) also decreased. The authors are to be congratulated on such a comprehensive and complete study. Compared with other reports,<sup>2,3,6</sup> their results also indicate less active intervention at less than 24 weeks and con-

sequent low survival, in keeping with the prevailing national philosophy. Above all else, the philosophy of the health care professionals and parents will determine survival at these low gestational ages. There is little consensus across Europe on the appropriateness of intervention at less than 25 weeks,<sup>8</sup> and previous reports<sup>6</sup> from Sweden indicate much higher survival rates down to 23 weeks with active intervention. Despite this, there is variation within Sweden itself,<sup>9</sup> and long-term outcomes seem as yet not to parallel improvements in survival.<sup>10</sup> Thus, attempts to use data such as those from EPIPAGE-2 at these extremely low gestational ages for counseling should be set in context. It is difficult to use data in which we do not know whether intervention was optimized for survival.

Clinicians need to be able to quote up-to-date and relevant information to parents facing the prospect of extremely low gestational age birth,<sup>11</sup> and much has been made about improved precision in risk. The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Network provides data on outcomes of infants born at low gestational ages, which vary with birth weight, fetal sex, and the use of corticosteroids.<sup>12</sup> This network provides an online calculator to refine this risk. For a parent facing a decision on what action the clinical staff should take during labor and after birth, these variations are somewhat irrelevant in the context of their child's birthplace. A more contentious issue is when to offer the woman choices about interventions for labor because not infrequently labor onset is rapid and progress to delivery swift. It is heartening to see that within EPIPAGE-2 most deaths that occurred were after redirection of care to palliation, presumably in the neonatal nursery after counseling of parents in a less stressful environment than during labor.

Given that these large studies are expensive, time-consuming, and challenging to perform, are they necessary and do we need to keep performing them? Could we not simply use local data to inform decisions? First, local data are subject to variation; when aggregate data were used during 4 years, the CIs of survival in my institution varied from 22% to 70% at 23 weeks of gestation and 55% to 88% at 24 weeks (N.M., unpublished data, 2014). Outcomes vary even more because numbers are smaller. Thus, use of national or regional data improves the precision of the estimate and provides a benchmark against which individual institutions can evaluate their own performance. Second, population studies can identify trends that can help plan and develop services. For example, in the United Kingdom, we have recently evaluated outcomes against the clinical setting in which the birth occurs, finding better sur-

vival for the fetus in labor and after delivery where birth occurs in an appropriate setting, with further improvement in hospitals that have a larger throughput.<sup>13</sup> Third, these data can help identify areas where practice may be improved or should be subjected to study. Obstetric factors are one such area<sup>11</sup>: one example might be the increasing trend to use cesarean section to deliver infants at extremely low gestational ages, which currently has an inconsistent evidence base in the literature. Fourth, each of these huge studies is not simply an exercise in survival and complications of neonatal care. All have important long-term outcomes that help explain and develop concepts of the key issues faced by preterm children as they age. The EPICure study, for example, is currently evaluating sur-

vivors at 19 years of age<sup>14</sup> to complete our neonatal education about the outcomes and consequences of our care.

How often are studies such as these required? I suggest the answer to this question is when we are able to convince funders of the need for them. Each of these studies will have great value outside simply reporting outcomes. Studies such as EPIPAGE-2 assist in the crystallizing of debates around the institution of care, settle important opinions about outcomes, tell us about the success or failure of our clinical interventions, define where research and change are required, set up key hypotheses for testing, and, importantly, provide reassurance for parents that decision making in this difficult area is subject to regular review and debate.

#### ARTICLE INFORMATION

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