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Morbidity and Mortality in Late-Preterm Infants: More Than Just Transient Tachypnea!

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Concern about higher morbidity in late-preterm (34^{0/7} to 36^{6/7} weeks) infants has led to a flurry of recent publications with largely the same conclusions: late-preterm infants are more prone to problems related to delayed transition and overall immaturity, and should therefore be treated differently than their more mature full term counterparts [1-5]. These observations have led to greater attention being paid to tracking short term morbidity, health care costs, hospital stays, and issues such as re-hospitalization [5]. However, widespread publicity has yet to make a measurable impact on the incidence of late prematurity; nearly three out of four preterm births occur at late-preterm gestations and this number is on the rise [6]. It is estimated that nearly 250,000 late-preterm births occurred in the US in 2004; and although the problem appears to be widespread, similar estimates from other nations are not readily available.

A broad range of neonatal complications has been documented in the growing body of literature on late-preterm infants. These problems include delayed lung fluid clearance (transient tachypnea of the newborn), respiratory distress syndrome, pulmonary hypertension, apnea, temperature instability, hypoglycemia, jaundice and poor feeding [6]. Little, however, is known about the long term impact of these “transitional issues” because there are no data repositories with information about outcomes and, in spite of growing concern about the vulnerability of the late-preterm brain to white matter injury, systematic developmental assessments are seldom performed.

These publications notwithstanding, the obstetric community is yet to fully embrace the public health impact of late prematurity. Late-preterm infants are considered functionally mature (hence the widespread use of the “near term” label) and there is a relative lack of attention to neonatal considerations when delivery at these gestations is being contemplated. Although women in preterm labor at gestations 33 weeks and less are routinely considered for tocolysis and antenatal steroids, they are candidates for neither if gestation has advanced by a few days and crosses over to the magical 34-week mark. These decisions appear oblivious to the fact that inaccuracies in the estimation of gestational age abound, and up to 50% of infants at 34 weeks gestation may require intensive care [1].

What then will it take to drive a concerted effort to tackle this problem? A good starting point will be the availability of reliable data about short and long-term outcome of late-preterm infants, and documentation of serious morbidity that could dispel the myth of the “transient” nature of late-preterm woes. Recent reports about the occurrence of serious complications such

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Editorial Focus

as hypoxic respiratory failure and kernicterus are good first steps, and compilation of accurate mortality statistics would be another [2,7]. In this issue of *The Journal*, Tomashek et al [8] attempt to close the gap in our understanding of differences in mortality between late-preterm and term infants. Using period linked birth-infant death files from 1995-2002, the authors analyzed overall and cause specific mortality rates for singleton late-preterm and term infants. The authors report that although significant declines in mortality were observed over the last decade for both groups of infants, the infant mortality rate for late-preterm infants was several-fold higher than that for term-infants. Late-preterm infants were particularly more likely to die in the early neonatal period compared to term infants from causes such as respiratory compromise, maternal complications of pregnancy and congenital anomalies.

The report by Tomashek et al [7] is being highlighted for several reasons. *First*, although their data clearly demonstrate a higher mortality burden related to birth at late-preterm gestations, the magnitude of the reported difference is particularly striking. Problems associated with the use of large data bases such as the one used by the authors notwithstanding, the low frequency of death in term and near-term infants precludes other methodological approaches including the use of smaller (but more detailed) local data sources for such analyses. This report underscores the need for prospective data collection to confirm the overall excess in mortality--information that is critical for affecting a change in allocation of resources and for an overall change in our approach to these neonates.

Second, this work sheds new light on the causes of death in late-preterm infants. For example, the reported high occurrence of congenital anomalies in late-preterm infants raises several questions that need to be addressed in future studies. Are fetuses with serious congenital anomalies more likely to be delivered early either spontaneously or electively, given the widespread practice of "controlled" delivery of an anomalous fetus? Does prematurity and lack of spontaneous labor add to the risk of death in infants with congenital anomalies? Are late-preterm infants at higher risk of death if infants with congenital anomalies are excluded? To address the last issue, the authors performed additional analysis of their data after excluding infants with any congenital malformation, deformation or chromosomal abnormality (ICD-10Q00-99) as the underlying cause of death. The differences in infant mortality between late-preterm and term infants were found to persist even with these exclusions, underscoring the inherent vulnerability of the late-preterm infant to serious morbidity and death.

There are several limitations to the methodology used and, as such, to any conclusions drawn from data linked to death certificates[8]. Death certificates lack information about contributing causes of death that could shed more light on diagnostic categories such as "atelectasis." Autopsy findings were also not available to ascertain diagnoses such as SIDS. Finally, data reported on gestational age may be subject to misclassification, although, as they argue, such errors should impact both sub-groups included in the analysis. However, the hypothesis generated by these data that now needs further testing is straightforward: Are late-preterm infants at higher risk for death than their term counterparts and, if so, why?

Overall, it should come as no surprise that the higher morbidity reported in late-preterm infants may be associated with an increase in mortality as well. What is surprising is the magnitude of the difference in death rates between late-preterm and term infants, given the perception of mild and transient nature of these problems. The findings should also foster debate around the rationale for preterm delivery, particularly when the decision to do so is based on soft indications. Although the data provide no direct link to the widespread practice of induction of labor and/or elective Cesarean sections, it raises questions about the recent rise in such practices, particularly in the face of uncertainty in accurate estimation of gestational age. As such, future occurrences of serious morbidity/death in electively delivered late-preterm infants where a clear indication for early delivery is lacking, should call for a thorough peer review of

the circumstances around delivery and the subsequent care of the neonate. Finally, there is an urgent need to study the role of strategies to enhance maturity of the late-preterm fetus, such as the use of antenatal steroids. Given the large number of deliveries at late-preterm gestations, the public health impact of such preventive strategies could be enormous.

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