Journal of Perinatology (2017) 37, 899–900

www.nature.com/jp

EDITORIAL

Cerebral palsy and asphyxia in 32–35 week preterm infants

Journal of Perinatology (2017) **37,** 899–900. doi:10.1038/jp.2017.78

The development of hypothermia as a therapy to reduce the impact of hypoxic–ischemic encephalopathy has been one of the great achievements in neonatal medicine of the twenty-first century. The approach, however, has been limited in its application to the term infant, as it has been discouraged in infants who are <35 weeks of gestational age (GA) at birth, pending further study.[1] This has raised the following questions: (1) What is the impact of HIE on the premature infant? (2) What is the actual biological cutoff at which hypothermia becomes more of a liability than a benefit?

In this volume of the *Journal of Perinatology*, Garfinkle *et al.*[2] report on their developmental analysis of children born at 32–35 weeks GA with documented birth asphyxia, as compared to those born at 36 or greater weeks of GA. Using the Canadian Cerebral Palsy (CP) Registry, they were able to review nearly 900 cases, and found that approximately 15% of the cases of CP could be attributed to suspected birth asphyxia. The clinical and imaging characteristics of the patients were reviewed, and comparisons were made based on GA. Perhaps not surprisingly, their findings differed for these two groups, providing yet additional evidence that the 'late-preterm infant' is a very different individual than the term infant, likely based on their stage of development and thus altered pathobiology.

The authors are persuasive in arguing that understanding how infants differ based on GA may shed light on alternative neuroprotective strategies that may uniquely protect the late-preterm infant, and lessen their burden from CP. A key difference is the preponderance of the preoligodendrocyte in the preterm infant. This immature cell line has been shown to be especially vulnerable to ischemic injury, making it a target of particular interest in strategies that may alter outcomes in the preterm infant.[3] Although infants born at <32 weeks GA are at risk for white matter injury ranging from punctate injuries to the cystic lesions associated with periventricular leukomalacia, this disease process becomes less important once myelination begins.[4,5]

The sentinel event underlying the suspected birth asphyxia also differed in the Canadian CP Registry, with the most common event occurring in the preterm population being placental abruption. Seizures during the first 72 h of life were less common in the premature infants. Of particular interest, the imaging characteristics were markedly different between the two groups. The term infants had evidence of near-total brain injury as delineated by MRI and/or ultrasound, whereas the preterm infants showed only isolated white matter injury. Of note, 40% of the preterm infants were found to have an intraventricular hemorrhage, a lesion not typically associated with infants >30 weeks of gestational age. This finding may explain in part why the premature infants also had a greater incidence of spastic diplegia (24%) when compared to their term counterparts (8%), odds ratio 1.8. It also begs the question of whether the thrombocytopenia that has been described in association with perinatal asphyxia plays a greater pathogenic role in the premature infant.[6]

As with all database surveys, unanswered questions remain that can be best approached using a prospective study design. Although the incidence of IVH is defined in the Canadian registry, the severity is not. Again, this raises the question of which is the greater contributor: asphyxia or IVH? The incidence of posthemorrhagic ventricular dilatation is not provided, nor do we know how many infants progressed to the point of requiring surgical intervention for hydrocephalus. What does seem clear, however, is that there is a group of late-preterm infants who are at risk for IVH, and who are not covered by current imaging screening guidelines.[7] Dissecting out the contribution of IVH to the outcomes of the late-preterm infant with suspected asphyxia will be important, as interventions designed to mitigate the effects of hypoxic–ischemic injury may not address the risk for IVH, and may even exacerbate it.

The work of Garfinkle *et al.*[2] answers some questions, but raises still more. Is hypothermia an appropriate intervention for the premature infant?[8] A current clinical trial being actively conducted by the NICHD Neonatal Research Network may provide some guidance as to whether hypothermia is appropriate for infants of 33–35 weeks GA (https://www.clinicaltrials.gov/ct2/show/NCT01793129; Higgins RD, personal communication).

There is a panoply of directions being explored for the diagnosis and management of HIE. The burgeoning area of neurocritical care for neonates has led to the creation of specialized NICU environments that are optimized for data collection and surveillance for neurologic sequelae, including real-time digital video and amplitude integrated electroencephalographic monitoring.[9] Novel technologies, such as positron emission tomography, which has shown that there is differential cerebral glucose metabolism in severe versus mild and moderate HIE, may provide objective evidence of the severity of the disease process and may provide useful triage criteria for various interventions.[10] Paradigm-shifting interventions, such as the use of umbilical cord stem cells to regenerate damaged neural tissues, are in the early stages of investigation, but show sufficient promise that we may soon be debating whether or not to bank cord blood samples for stem cells in HIE patients.[11] Should HIE be anticipated, and interventions initiated with the mother before birth, such as the use of melatonin as an antioxidant to reduce oxidative stress?[12] Lastly, are there other infants who would benefit from hypothermia and who are not currently within the treatment criteria, such as those with chromosomal abnormalities, stroke or postnatal collapse?[13]

Goals with the aim of improving our understanding of the pathobiology of hypoxic–ischemic encephalopathy and its optimal treatment must continue, and remain a key challenge for neonatologists and neurologists of our day. Garfinkle *et al.*[2] have ably reminded us that asphyxia is not the exclusive province of the term infant, and that we must be attentive to the risks for the late-preterm infant, as well.

CONFLICT OF INTEREST

The author declares no conflict of interest.

De-Ann M Pillers
Department of Pediatrics, University of Wisconsin, Madison, WI, USA
E-mail: pillersd@pediatrics.wisc.edu

REFERENCES

1 Committee on Fetus and Newborn, Papile LA, Baley JE, Benitz W, Cummings J, Carlo WA, Eichenwald E *et al.* Hypothermia and neonatal encephalopathy. *Pediatrics* 2014; **133**: 1146–1150.

2 Garfinkle J, Wintermark P, Shevell MI, Oskoui M and on behalf of the Canadian Cerebral Palsy Registry. Children born at 32 to 35 weeks with birth asphyxia and later cerebral palsy are different from those born after 35 weeks. *J Perinatol* (this issue).
3 Back SA, Han BH, Luo NL, Chricton CA, Xanthoudakis S, Tam J *et al.* Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. *J Neurosci* 2002; **22**: 455–463.
4 Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *J Neurosci* 2001; **21**: 1302–1312.
5 Back SA, Rivkees SA. Emerging concepts in periventricular white matter injury. *Semin Perinatol* 2004; **28**: 405–414.
6 Christensen RD, Baer VL, Yaish HM. Thrombocytopenia in late preterm and term neonates after perinatal asphyxia. *Transfusion* 2015; **55**: 187–196.
7 Ment LR, Bada HS, Barnes P, Grant PE, Hirtz D, Papile LA *et al.* Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2002; **58**: 1726–1738.
8 Higgins RD, Shankaran S. Hypothermia: novel approaches for premature infants. *Early Hum Dev* 2011; **87**(Suppl 1): S17–S18.
9 Glass HC, Bonifacio SL, Peloquin S, Shimotake T, Sehring S, Sun Y *et al.* Neurocritical care for neonates. *Neurocrit Care* 2010; **12**: 421–429.
10 Shi Y, Zhao JN, Liu L, Hu ZX, Tang SF, Chen L *et al.* Changes of positron emission tomography in newborn infants at different gestational ages, and neonatal hypoxic-ischemic encephalopathy. *Pediatr Neurol* 2012; **46**: 116–123.
11 Aly H, Mohsen L, Badrawi N, Gabr H, Ali Z, Akmal D. Viability and neural differentiation of mesenchymal stem cells derived from the umbilical cord following perinatal asphyxia. *J Perinatol* 2012; **32**: 671–676.
12 Marseglia L, D'Angelo G, Manti S, Reiter RJ, Gitto E. Potential utility of melatonin in preeclampsia, intrauterine fetal growth retardation, and perinatal asphyxia. *Reprod Sci* 2016; **23**: 970–977.
13 Thoresen M. Who should we cool after perinatal asphyxia? *Semin Fetal Neonatal Med* 2015; **20**: 66–71.