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COMMENT

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Larger brain volumes at term-equivalent age in infants born preterm: an alternative explanation

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In a publication entitled "Serum docosahexaenoic acid levels are associated with brain volumes in extremely preterm born infants," published in this issue of *Pediatric Research*, Hortensius et al.[1] compare volumes of six brain regions at term-equivalent age (TEA) to serum phospholipid (PL) docosahexaenoic acid (DHA) in the first 28 days of life. The DHA results were collected in an earlier randomized controlled trial that assigned infants born <28 weeks gestation to either SMOFlipid® or Clinoleic® as a source of parenteral nutrition[2]. The primary trial was designed to evaluate the effect of long-chain *n*-3 fatty acids in fish oil added to SMOFlipid®, namely DHA and eicosapentaenoic acid (EPA), on morbidities in extremely premature infants. In this secondary analysis, they conclude that serum PL DHA (area under the curve) in the first 28 days of life is associated with greater total, cortical gray matter, deep gray matter, cerebellar and white matter volumes at TEA. However, gestational age (GA) at birth was highly correlated with serum PL DHA, and when the authors attempted to include GA at birth in the final multivariable model for total and regional brain volumes, the model became "unstable," and GA was not included. In Appendix 1 they report a model in which GA replaces serum PL DHA. That model has a nearly identical ability to predict brain volumes.

Had the authors asked the question: "How does GA affect total and regional brain volumes at TEA?," they would have concluded that being born later was an advantage for larger brain volumes. Therefore, an alternative explanation needs to be considered, i.e., that being born at an earlier GA explains smaller brain total and regional volumes at TEA. In fact, many published reports link smaller brain size and smaller size in some brain regions with preterm birth. Here are only two that seem particularly relevant. Iwata et al.[3] compared regional brain sizes in infants born at a range of GAs from 24 to 42 weeks and found a linear relationship between GA at birth and brain size at TEA. Walsh et al.[4] reported that infants born between 32 and 36 weeks GA had smaller brain biparietal diameter, corpus callosum, basal ganglia and thalami, and cerebellum at TEA than did infants born at term.

Moreover, there is a plausible explanation linking GA to smaller brain volume. Tan et al.[5] studied infants born <29 weeks GA and found that lower energy intake at 28 days predicted smaller total brain volumes at TEA. Lower GA at birth is well known to compromise energy intake in the first 28 days after birth.

Smaller brain volumes in infants born preterm have been reported to persist long after TEA. In a case-controlled study of regional brain volumes, Peterson et al.[6] compared 8-year-old children who were born as early as 26 weeks GA to children born at term and found smaller volumes in multiple brain regions including the cerebellum and corpus callosum. Smaller volumes were directly proportional to how early the children were born. Another case-controlled study in young adults aged 19–20 years found that those born at a mean of 30 weeks GA had a smaller subcortical white matter and gray matter volumes compared to young adults born at term. These investigators also linked white and gray matter volumes to GA at birth[7].

It appears Hortensius et al.[1] chose serum PL DHA as the variable of interest in relation to brain volume because infants in the parent study were assigned to parenteral lipids that varied in their content of DHA. In the first 28 days (and up to 32 weeks expected gestation), the SMOFlipid® group did have a small but significantly higher serum PL DHA compared to Clinoleic®; however, the authors report that brain volumes did not differ between the groups[1]. The absence of an effect of the randomization on brain volume despite an increase in serum PL DHA with SMOFlipid could be used to argue that something other than serum PL DHA is the primary factor influencing brain volumes. In addition, the amount of DHA received in the first 28 days was small relative to the amount of enteral DHA received by TEA in both groups. The fact that DHA intake to TEA did not enter the model predicting brain volumes is another argument against serum PL DHA as the true predictor of brain volumes.

We agree with the author's statement that providing DHA to preterm infants is important for early brain development. Regardless of whether DHA increases brain size, the first studies that provided formulas containing DHA to preterm infants found higher cortical visual acuity[8] and cognition (infant attention)[9] in the first year of life compared to preterm infants fed the preterm formulas available at that time, which did not contain DHA. A randomized trial to test if DHA can influence brain volume could still be done; however, because most preterm infants now receive DHA, it would need to be a superiority trial in which one group received a much larger amount of DHA.

The rapid decline in DHA status after preterm birth was first reported 35 years ago[10]. These investigators have also reported that infants had higher serum PL DHA at birth than after 7 days, with a more rapid decline in infants born at lower GA[2]. It is reasonable to suggest that the more rapid decline in the earliest born infants occurs because the preferential transfer of DHA to the fetus that occurs in the last trimester of pregnancy[11] leaves them with a larger DHA deficit. This may explain the correlation of DHA status with GA.

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In the end, this is an observational study. GA and serum PL DHA are highly correlated, but it cannot be concluded that either causes lower brain volumes at TEA. We have only tried to make the point that there is substantial observational evidence linking lower GA to lower brain volumes, evidence that is lacking for DHA status in the first 28 days after preterm birth.

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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