

Journal Pre-proof



Effects of early iron supplementation on later neurodevelopmental outcomes in preterm infants

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Letter to the Editor

**Effects of early iron supplementation on later neurodevelopmental
outcomes in preterm infants**

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Dear Editor,

German et al (1) address an important and clinically relevant research topic - the effects of early iron supplementation on later neurodevelopmental outcomes in preterm infants. It was surprising that the variation in enteral iron intakes was large, from 0 to > 500 mg/kg during the first 60 days of life (mean [SD] 3.0 [1.9] mg/kg/day), especially since the PENUT study provided specific guidance on iron supplementation, recommending 6 mg/kg/day when infants were on > 100 mL/kg/d of enteral feeds. What are the main factors affecting this huge variation in iron intakes?

If the study centers attempted to follow the guidelines above, we assume that an important reason for lower iron intakes was prolonged feeding difficulties, which is typically seen in the most severely ill patients. Enteral feeds were not adjusted for, despite the fact that higher enteral feed volumes are associated with increased brain volumes (2) and better neurodevelopmental outcomes (3), which has also been shown specifically for human milk intakes (4). The authors adjusted for some morbidity related variables but not for gestational age or birth weight as continuous variables, or days on respirator, which is a more robust marker of disease severity.

Another reason to question the conclusion that an iron intake of > 4 mg/kg/d would improve cognitive development, especially in EPO treated infants, is that there was no effect of the PENUT intervention which delivered both EPO and a higher iron intake to the intervention group (mean 4.8 vs 3.6 mg/kg/day) (5).

Based on these uncertainties, we suggest that it might be prudent not to give firm recommendations on iron supplementation of extremely preterm infants based on the current study.

- 1 German KR, Vu PT, Comstock BA, et al. Enteral Iron Supplementation in Infants Born Extremely Preterm and its Positive Correlation with Neurodevelopment; Post Hoc Analysis of the Preterm Erythropoietin Neuroprotection Trial Randomized Controlled Trial. *J Pediatr* 2021;238:102-09 e8.

- 2 Coviello C, Keunen K, Kersbergen KJ, et al. Effects of early nutrition and growth on brain volumes, white matter microstructure, and neurodevelopmental outcome in preterm newborns. *Pediatr Res* 2018;83(1-1):102-10.
- 3 Tottman AC, Bloomfield FH, Cormack BE, et al. Sex-specific relationships between early nutrition and neurodevelopment in preterm infants. *Pediatr Res* 2020;87(5):872-78.
- 4 Lapidaire W, Lucas A, Clayden JD, et al. Human milk feeding and cognitive outcome in preterm infants: the role of infection and NEC reduction. *Pediatr Res* 2021.
- 5 Juul SE, Comstock BA, Wadhawan R, et al. A Randomized Trial of Erythropoietin for Neuroprotection in Preterm Infants. *N Engl J Med* 2020;382(3):233-43.

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