Randomized Controlled Trial of Iron-Fortified versus Low-Iron Infant Formula: Developmental Outcomes at 16 Years

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Objectives: To test differences in cognitive outcomes among adolescents randomly assigned previously as infants to iron-fortified formula or low-iron formula as part of an iron deficiency anemia prevention trial. Study design: Infants were recruited from community clinics in low- to middle-income neighborhoods in Santiago, Chile. Entrance criteria included term, singleton infants; birth weight of ≥3.0 kg; and no major congenital anomalies, perinatal complications, phototherapy, hospitalization >5 days, chronic illness, or iron deficiency anemia at 6 months. Six-month-old infants were randomized to iron-fortified (12 mg/L) or low-iron (2.3 mg/L) formula for 6 months. At 16 years of age, cognitive ability, visual perceptual ability, visual memory, and achievement in math, vocabulary, and comprehension were assessed, using standardized measures. We compared differences in developmental test scores according to randomization group. Results: At the follow-up assessment, the 405 participants averaged 16.2 years of age and 46% were male. Those randomized to iron-fortified formula had lower scores than those randomized to low-iron formula for visual memory, arithmetic achievement, and reading comprehension achievement. For visual motor integration, there was an interaction with baseline infancy hemoglobin, such that the iron-fortified group outperformed the low-iron group when 6-month hemoglobin was low and underperformed when 6-month hemoglobin was high. Conclusions: Adolescents who received iron-fortified formula as infants from 6 to 12 months of age at levels recommended in the US had poorer cognitive outcomes compared with those who received a low-iron formula. The prevention of iron deficiency anemia in infancy is important for brain development. However, the optimal level of iron
supplementation in infancy is unclear. Trial registration: Clinicaltrials.gov: NCT01166451.