ABSTRACT

Background: Iron deficiency anemia (IDA) is a global public health problem, affecting an estimated 51% of children below 4 years of age in developing countries and 12% in developed countries. There is a well-known association between IDA and delayed neurodevelopment in infants. For many reasons, breast milk is important for the infant, and WHO and other organizations recommend breast-feeding for at least one year. However, due to the low iron content of breast milk and high iron requirements for growth, infants who are breast-fed for longer than 4-6 months need iron from additional sources. This is why in many countries iron supplementation, as iron drops, is recommended to breast-fed infants who do not consume sufficient amounts of iron-fortified foods.

Study design: Since the effects of such supplementation are largely unknown, we performed a randomized, controlled, double-blind study of 263 healthy, term infants who received ferrous sulfate drops (starting at 4 or 6 months) or placebo drops. The infants were exclusively breast-fed to 6 months and partially to 9 months. Swedish (n=121) and Honduran (n=142) infants were studied to allow assessment of the effects of iron supplementation across a wide range in iron status. Blood samples were obtained at 4, 6 and 9 months. Iron absorption was studied in 25 infants, using a stable isotope method.

Results: There was a low prevalence of IDA (< 3%) in Swedish infants at 9 months of age. In Honduras, however, 29% of the infants had IDA at 9 months of age, and this proportion was reduced to 9% by giving prophylactic iron drops from 4 or 6 months. Unexpectedly, iron supplementation significantly reduced longitudinal growth and this effect was more pronounced in Swedish infants. Swedish infants, iron supplemented from 4 months, also showed a significant reduction in head growth. At 6 months, fractional iron absorption from human milk was 16%. At 9 months, absorption was still low in iron supplemented infants but had increased to 37% in unsupplemented infants. Dietary iron intake was shown to be an important negative regulator of iron absorption in these infants. This adaptation of iron absorption may explain why we found no effect of complementary food iron intake on iron status. Boys had a 10-fold higher risk for being diagnosed with IDA. The sex difference could not be explained entirely by differences in birth weight, weight gain or complementary food intake. Hemoglobin (Hb) response to iron was shown to be a poor indicator of IDA at 4 months because iron supplemented infants at this age responded with an increase in Hb regardless of initial iron status. New reference values are presented for iron status variables based on iron-replete, breast-fed infants. For some variables, 2 SD cutoffs at 9 months were significantly lower than conventional cutoffs: Hb < 100 g/L and ferritin < 5 μg/L, instead of Hb < 110 g/L and ferritin < 10-12 μg/L.

Conclusions: Iron supplementation effectively prevents IDA in a population with a high prevalence of this condition. In low-risk or mixed populations, routine iron supplementation of breast-fed infants should be avoided because of possible negative effects on growth. Iron requirements of term, breast-fed, Swedish infants are likely to be lower than previously believed. It is necessary to re-evaluate the laboratory criteria for IDA in infants, especially in relation to clinical symptoms such as impaired neurodevelopment. Since iron deficiency is a global public health problem and since the first year of life is a crucial period for growth and development of the central nervous system, this issue deserves high priority.