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Iron supplements and oxidative stress in very low birth weight infants

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To the Editor

We congratulate Brække et al on their recent report.¹ The practice in Norway of administering iron supplementation to very low birth weight (VLBW) infants with 18 mg/day of ferrous fumarate from age 6 weeks is based on a 1955 study of 26 infants by Gairdner et al,² in which 50% received 60 mg of ferrous sulfate 3 times a day from age 2 or 3 weeks and 50% received the same dose of iron when their hemoglobin level fell to 11 g/100 mL. Gairdner et al concluded that iron supplements given to VLBW infants starting at age 3 weeks could mitigate anemia.

Today, VLBW infants who survive are more premature, have poorer antioxidant defense systems,^{3,4} and receive more red cell transfusions. Brække et al have correctly raised the question of whether it is wise practice to continue high iron supplementation in VLBW infants. We would like to comment on whether their findings should affect the clinical care of VLBW infants in the United States.

Brække et al studied healthy and stable VLBW infants with a median weight of 1785 g at age 5 weeks. They excluded infants requiring >30% oxygen and/or mechanical ventilation. However, it is the “sick” and unstable VLBW infants who are at higher risk for developing severe bronchopulmonary dysplasia, necrotizing enterocolitis, and retinopathy of prematurity. Oxidative stress contributes to each of these morbidities.⁵ Administration of ferrous iron, which can initiate the oxidation cascade,⁶ may result in overloaded antioxidation capacity. Studies of these sick and unstable infants are needed to provide information on oxidative stress due to iron supplementation.

The authors draw their conclusions based on 1 week of iron supplementation. The question remains open as to whether oxidative stress from high doses of iron supplements would increase with longer exposure periods that reflect real life situations.

In this study, the median plasma ferritin level dropped from 84 to 59 µg/L between weeks 5 and 6 and increased to 63 µg/L by the end of week 7. None of the infants had iron-deficiency anemia, defined as plasma ferritin level <10 µg/L.⁷ Most of the infants with birth weight <1000 g had received red cell transfusions, which resulted in higher serum ferritin levels before the initiation of iron supplementation. Thus, the risk of iron-deficiency anemia in

VLBW infants would depend on red cell transfusion policy of each neonatal intensive care unit.

The authors state that the infants in their study were all fed human milk (HM). The percentage of infants who receive HM exclusively varies widely in the United States; nearly 75% receive some breast milk, with 30% still receiving HM at discharge.⁸ VLBW infants who are not fed HM are fed iron-fortified (12 to 15 mg/L ferrous sulfate) formula from the very first feed. In addition, these infants receive iron supplements (3 to 6 mg/kg/day or more of ferrous sulfate), even though the recommended dose of iron is 2 to 3 mg/kg/day from age 8 weeks.⁹ Thus, formula-fed infants receiving supplementation with 6 mg/kg/day of ferrous sulfate would receive a dose of iron similar to that given in standard practice in Norway (7.7 to 15.9 mg/kg; Table). However, the infants in Norway would receive ferrous fumarate rather than the ferrous sulfate given to infants in the United States. We have shown that ferrous fumarate produces minimal or no oxidative stress in vitro compared with ferrous sulfate.¹⁰

Lactoferrin in HM attenuates iron-induced oxidation products in vitro.¹⁰ Because all of the infants in the study of Brække et al were fed HM, the level of iron-induced oxidative stress would be expected to be attenuated by lactoferrin.

At age 5 weeks, 9 of the infants in the study weighed <1500 g and received vitamin E; by the end of the study (week 7), only 5 infants were receiving vitamin E. Despite this supplementation, median plasma α -tocopherol level decreased from 1.2 mg/dL at week 5 to 0.88 mg/dL at week 7 (normal, 1 to 3 mg/dL). Whether most or all VLBW infants would be vitamin E-deficient (plasma levels <1 mg/dL, ie, <23 μ mol) with long-term high iron supplementation is unknown.

In view of the foregoing, results of the study by Brække et al, although a necessary first step, do not provide sufficient evidence for US neonatologists to increase iron supplements to VLBW infants. Future collaboration between neonatologists and free-radical biologists may help address the question of when to start iron supplementation in VLBW infants and the dosage to use.

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Table

The amount of ferrous iron supplements that a hypothetical 1.5-kg preterm infant receiving 150 mL/kg/day of enteral feeds would receive in the United States

Formula/breast milk	Iron supplements as ferrous sulfate, mg/kg	Total iron, mg/kg/day
Preterm infant formula (20 cal/oz; 12.2 mg/L of ferrous iron)	3 or 6	7 to 10
Premature infant formula (24 cal/oz; 15 mg/L of ferrous iron)	3 or 6	7.8 to 10.8
Breast milk + Enfamil HMF (22 to 24 cal/oz; 7.2 to 14.4 mg/L of ferrous iron)	3 or 6	5.3 to 8.3 (22 cal/oz) or 7.6 to 10.6 (24 cal/oz)
Breast milk + Similac HMF (22 to 24 cal/oz; 3 to 4.5 mg/L of ferrous iron)	3 or 6	3.9 to 4.1 (22 cal/oz) or 6.9 to 7.1 (24 cal/oz)
Similac Neosure (22 cal/oz; 13.4 mg/L of ferrous iron)	3 or 6	7.3 to 10.3
Enfacare LIPIL (22 cal/oz; 13.4 mg/L of ferrous iron)	3 or 6	7.3 to 10.3

The ferrous iron is added as ferrous sulfate.