E–deficient (plasma levels <1 mg/dL, ie, <23 μmol) 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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REFERENCES

1. Brække K, Bechensteen AG, Halvorsen BL, Blomhoff R, Haaland K, Staff AC. Oxidative stress markers and antioxidant status after oral iron supplementation to very low birth weight infants. J Pediatr 2007;151:23-8.
2. Gairdner D, Marks J, Roscoe JD. Blood formation in infancy, part IV: the early anaemia of prematurity. Arch Dis Child 1955;30:203-11.
3. Bracci R, Buonnocore G. The antioxidant status of erythrocytes in preterm and term infants. Semin Neonatol 1998;3:191-7.
4. Gopinathan V, Miller NJ, Milner AD, Rice-Evans CA. Bilirubin and ascorbate antioxidant activity in neonatal plasma. FEBS Lett 1994;349:197-200.
5. Saugstad OD. Oxidative stress in the newborn: a 30-year perspective. Biol Neonate 2005;88:228-36.
6. Qian SY, Buettner GR. Iron and dioxygen chemistry is an important route to initiation of biological free radical oxidations: an electron paramagnetic resonance spin-trapping study. Free Radic Biol Med 1999;26:1447-56.
7. Fomon SJ. Iron In: Fomon SJ, editor. Nutrition of Normal Infants. St. Louis: Mosby; 1993. p 239-60.
8. Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Wright LL, Langer JC, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. Pediatrics 2006;118:e115-23.
9. American Academy of Pediatrics Committee on Nutrition. Nutritional needs and feeding of premature infants. Pediatrics 1985;75:976-86.
10. Raghuveer TS, McGuire EM, Martin SM, Wagner BA, Rebouche CJ, Buettner GR, et al. Lactoferrin in the preterm infants' diet attenuates iron-induced oxidation products. Pediatr Res 2002;52:964-72.

Reply

To the Editor:

We are grateful for Raghuveer and Buettner's valuable comments on our article. We wish to point out that we have not suggested any alteration in practice, but have performed an evaluation of current clinical practice on iron supplementation. Rather than suggesting higher doses or earlier introduction of iron, we would support the practice of feeding preterm infants human milk, which in vitro ameliorates a pro-oxidant effect of iron.[1] We encourage further studies in this complex field to ensure rational procedures that are optimal according to updated knowledge, with benefits for the developing infant.

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REFERENCE

1. Raghuveer TS, McGuire EM, Martin SM, Wagner BA, Rebouche CJ, Buettner GR, et al. Lactoferrin in the preterm infant's diet attenuates iron-induced oxidation products. Pediatr Res 2002;52:964-72.

ABCA3 mutation and pulmonary hypertension: A link with alveolar capillary dysplasia?

To the Editor:

We read with interest the article by Kunig et al[1] reporting a newborn with homozygous *ABCA3* mutation presenting as pulmonary hypertension (PH) We recently observed an infant born at term with mild respiratory symptoms but severe PH who carried a single *ABCA3* missense mutation. This patient was admitted at 3 months for persistent hypoxemia since birth and suprasystemic right ventricular pressure. Lung biopsy revealed interstitial thickening, type II pneumocyte hyperplasia, and intra-alveolar material accumulation, along with a decreased number of pulmonary capillaries centralized in the alveolar septae (Figure A) and failing to make contact with type I pneumocytes (Figure B). Most of the lamellar bodies in the type II pneumocytes appeared to be smaller than normal and more electron dense with a denser core, coexisting with multivesicular bodies and lamellar bodies that appeared normal, albeit reduced in number (Figure C). A new monoallelic *ABCA3* missense mutation (A501E) was found, together with 2 polymorphisms of the *SFTP-B* and *SFTP-C* genes (c392t and g577a, respectively). PH persisted despite treatment with oxygen and inhaled nitric oxide through nasal prongs plus oral sildenafil, and the child died of heart failure at age 8 months in another hospital.

Our case exhibited a combination of histological/ultrastructural aspects suggestive of *ABCA3* deficiency with vascular features usually found in alveolar capillary dysplasia (ACD).[2,3] These capillary anomalies likely underlie PH. Whether they derive directly from the single *ABCA3* mutation, from an *ABCA3* mutation in the second allele that was not identified, from associated mutations of other genes (compound heterozygosity), or from nongenetic factors is unknown. Although *ABCA3* deficiency is a recessive disease, monoallelic mutations have been reported in infants with

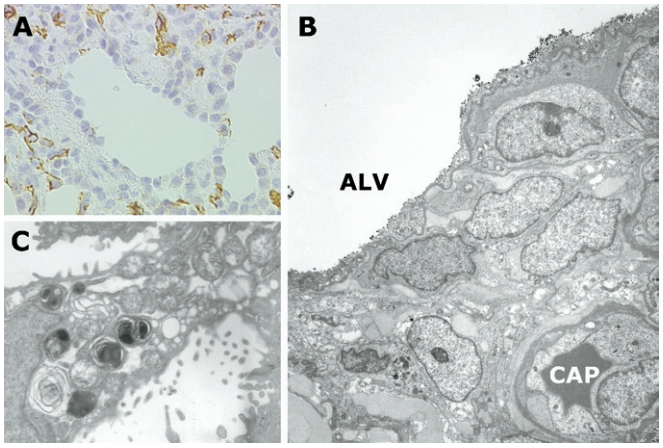

Figure. **A,** Pulmonary capillaries centralized in the interalveolar septae and reduced in number compared with controls (CD31 immunostaining; original magnification 63×). **B,** Rare capillaries separated from the alveolar lumen by several cell layers and failing to make contact with the type I cell basal membrane (original magnification 2500×). **C,** Transmission electron microscopy image showing lamellar bodies that are smaller and denser than normal, with small, disorganized concentric surfactant layers and 1 or 2 dense cores (Karnowsky's fixed, osmium tetroxide postfixed, lead citrate, and uranyl acetate stain; original magnification 6300×).

interstitial lung disease.[4-6] Our observations suggest that ACD, the genetic causes of which are unknown, may be related to *ABCA3* deficiency and support the authors' conclusions that patients with unexplained PH should be investigated for mutations in surfactant-related genes, because the clinical spectrum of these rare diseases is only partially known.

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REFERENCES

1. Kunig AM, Parker TA, Nogee LM, Abman SH, Kinsella JP. *ABCA3* deficiency presenting as pulmonary hypertension of the newborn. J Pediatr 2007;151:322-4.
2. Galambos C. Modelling alveolar capillary dysplasia. Circ Res 2004;95:e35.
3. Sen P, Thakur N, Stockton DW, Langston C, Bejjani BA. Expanding the phenotype of alveolar capillary dysplasia (ACD). J Pediatr 2004;145:646-51.
4. Yokota T, Matsumura Y, Ban N, Matsubayashi T, Inagaki N. Heterozygous *ABCA3* mutation associated with non-fatal evolution of respiratory distress. Eur J Pediatr 2008;167:691-3.
5. Bullard JE, Wert SE, Whitsett JA, Dean M, Nogee LM. *ABCA3* mutations associated with pediatric interstitial lung disease. Am J Respir Crit Care Med 2005;172:1026-31.
6. Bullard JE, Nogee LM. Heterozygosity for *ABCA3* mutations modifies the severity of lung disease associated with a surfactant protein C gene mutation. Pediatr Res 2007;62:176-9.