Iron Deficiency's Long-Term Effects

An Interview with Pediatrician Betsy Lozoff

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Abstract: Betsy Lozoff is among the world's leading experts on iron deficiency and its effects on infant brain development and behavior. Iron deficiency is the most common single nutrient disorder in the world, affecting more than half of the world's infants and young children. Research by Lozoff and others has shown that there are long-lasting developmental disadvantages among children who experienced severe, chronic iron deficiency as infants—disadvantages that are not corrected by giving iron later.

Council Member **Betsy Lozoff**, a developmental-behavioral pediatrician, is a professor of pediatrics in the Department of Pediatrics and Communicable Diseases at the University of Michigan Medical School and former director of the University's Center for Human Growth and Development. Her research focuses on iron deficiency anemia and infant behavior, primarily in developing countries, and the health and development of children who grow up in poverty in the U.S. Her recent research seeks to relate behavioral changes to the effects of iron deficiency on the developing brain. She has served on several review panels for the National Institutes of Health and the National Institute of Child Health and Human Development, as well as on the Executive Council of the Society for Developmental and Behavioral Pediatrics. She was a member of the Committee on Integrating the Science of Early Childhood Development for the Institute of Medicine and the National Research Council of the National Academy of Sciences.

For many years, you have studied the link between iron deficiency in children and their long-term health and development. What can you tell us about that connection and how it affects the growing brain's architecture?

We know that the human body needs iron to perform some of the most basic and essential functions. It needs iron to manufacture hemoglobin—the protein in red blood cells that carries oxygen throughout the body. It needs iron for proper muscle function, too. And—most relevant to this discussion—the body needs iron to carry out many critical processes in our brain and central nervous system.

When it comes to the growing brain, we're learning pretty definitively that the right level of iron is required for healthy neurotransmission, or the way the brain sends and receives "signals" from one area to another. Iron

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is essential for myelination—the process by which the brain produces a fatty insulation around the nerves. The insulation helps speed transmission of electrical signals. Based on studies of lab animals, we know iron has clear effects on the function of dopamine and probably serotonin, two brain chemicals that help send and receive signals (neurotransmitters) and have many roles in the brain. When iron deficiency anemia occurs in the young animal, important changes in both myelin and neurotransmitters persist to adulthood, despite iron therapy in infancy. We have to make a bit of a leap, but we can say that the behavioral changes we see in children who had iron deficiency in infancy are consistent with the brain effects we're finding in animals.

Children who suffered iron-deficiency anemia as infants have evidence of brain differences 10 years later.

Iron-deficiency anemia is considered the most common nutritional disorder in the world today, but we've managed to dramatically reduce its incidence among infants in the United States. What are some proven solutions?

In the U.S. and most economically developed countries, we have dramatically reduced anemia and iron deficiency through a few widespread interventions. From a clinical standpoint, this is a problem that can be solved if the community makes it a priority.

As late as the 1970s, we in the U.S. had levels of iron deficiency in infants on a par with much of the developing world. Federal government programs like Food Stamps and WIC (supplemental nutrition for Women, Infants and Children) started to make a big difference. In addition, baby formula companies started producing and marketing iron-fortified formula, prompted largely by calls from the American Academy of Pediatrics. Major cereal companies began adding iron to baby cereals. More vitamin C (also known as ascorbic acid, which enhances the body's ability to absorb iron from the intestines) was added to infant foods. There was a big effort to encourage breast feeding; the iron in breast milk is easily absorbed. Another solution for infants and children at greater risk of iron deficiency is the use of iron-fortified drops, also readily available. Together, these interventions have worked well for U.S. children.

Your work with children in Costa Rica and Chile has yielded very important findings.

We've now been following our research group of children in Costa Rica for more than 20 years. All those who had iron deficiency in infancy were treated with a closely supervised full course of iron therapy, which corrected all cases of iron-deficiency anemia.

And here's what we've been learning. When it comes to their motor development, children who had chronic, severe iron deficiency in infancy started with lower motor functioning and stayed lower over time; there's no evidence they catch up with their peers. In terms of social-emotional functioning, in early adolescence their parents and teachers rated them as showing significant symptoms of anxiety, depression, and inattention. At ages 11 to 14, the proportion repeating a grade in school was twice that of children who had good iron status in infancy. In terms of cognitive skills, the evidence is especially troubling: the gap in test scores actually increased over time. By late adolescence, the gap was bigger, regardless of whether they started with low or high scores as babies. The cognitive gap was also worse for those children from the most disadvantaged families who also had chronic, severe iron deficiency in infancy.

In Chile, we're finding that even after treatment for a year with iron drops, children who suffered iron-deficiency anemia as infants have evidence of brain differences 10 years later. Using electrophysiologic tests, we've been able to "look" into their brains and find that electrical signals move more slowly through their auditory and visual systems. Both the Costa Rican adolescents at 19 years and the Chilean children at 10 years who were treated for severe, chronic iron deficiency in infancy do worse on higher-level cognitive tests shown by functional magnetic resonance imaging (fMRI) to involve specific neural circuits where dopamine is the major neurotransmitter.

These long-term effects make us even more worried about how they'll do in adulthood. So we are looking at how the consequences of early iron deficiency might impact the kinds of jobs the Costa Rican subjects get as young adults, how much money they earn, and what kinds of relationships they establish. We hope to do the same for the Chile sample.

So clearly the implications are quite serious.

The evidence is certainly accumulating: There are effects of iron deficiency that are not reversed with iron therapy. It's very important to prevent the brain from being iron deficient in the first place—during its most sensitive time of development, in early childhood.

And there's a great deal at stake. By failing to solve this problem for literally millions of youngsters around the globe, aren't we risking that they won't meet their full potential? And what about the potential of the nations where they live? Some economists have even suggested that wide-scale iron deficiency—and the related problems of poor school performance and lower productivity—can have a major effect on a nation's entire economy and economic development.

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In our field, there are still important unanswered questions about when and how much to intervene. We still don't know things like when it's best to test for iron deficiency anemia, whether iron deficiency without anemia has ill effects, or how early and how long to give iron to improve effects on brain and behavior. We do think we'll be able to answer these questions in the coming years.

Another thing we're really looking at now is the effect of a mother's iron deficiency during pregnancy on the baby's brain and behavior. Because the body produces more blood during pregnancy for the placenta and the baby, there's an increased need for iron for both mother and baby, and a good diet alone can't always meet that need. So this is a huge question, since it's estimated that more than 50 percent of mothers in developing countries are anemic during pregnancy and iron deficiency in pregnancy is a problem everywhere.

What about children in the United States? Are there implications here at home, too?

It's important to remember that this problem doesn't affect the developing world alone. Even in the United States, iron deficiency remains a major public-health problem for infants. Despite all of our advances, we still see iron-deficiency anemia in 5 percent of poor Black and Hispanic infants and toddlers, and much higher levels of iron deficiency without anemia in some subgroups, such as Mexican-American children. Interestingly, these groups are at greater risk of iron deficiency regardless of their social and economic status, which suggests differences in infant diets or more iron deficiency during pregnancy may have a lot to do with the problem.

Recently, we've been studying infants from a poor area in Detroit, using brain-based measures. And we're finding that iron-deficient anemic infants are worse in their motor coordination and motor sequencing. And once again, we're seeing social-emotional differences—iron-deficient anemic infants seem more shy or hesitant, less engaged, less positive. We're also studying the infants with "event-related potentials" (ERPs)—a way of looking at the brain's activity in response to different stimuli—together with my National Scientific Council on the Developing Child colleague Chuck Nelson.

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It sounds as though solutions to this pervasive health problem are within reach. Where are the areas of greatest promise?

Yes, we've made great strides in much of the industrialized world. But in many countries where iron deficiency is widespread, pediatricians and public health policy makers are looking for inexpensive ways to prevent iron deficiency in babies, at the same time avoiding anything that might interfere with breastfeeding, which is so important for infant health and development. In many situations, iron-fortified formula or iron-fortified commercial infant foods are not good solutions. But now there are some promising new developments. Scientists have been working to develop grains that have better iron absorption. Other efforts, for example in the Philippines and elsewhere, aim to fortify plain white rice with valuable nutrients, including iron. Yet other countries, like Vietnam, are fortifying other staple foods, such as fish sauce.

For infants, an approach I think holds great promise is home-fortification with something called "sprinkles." A powdered, tasteless form of iron (mixed with vitamin C and other vitamins and minerals) can be provided in colorful little packets (like for sugar or sugar substitutes). They are designed to be sprinkled or stirred, one dose at a time, into any food the baby or toddler already eats. Studies by Dr. Stanley Zlotkin and his Canadian research team—in Ghana and Mongolia, for example—show the approach is very effective. It's affordable and avoids many of the problems (like bitter taste or discoloration) associated with other approaches. Iron sprinkles aren't commercially available yet, but the World Health Organization and other organizations have taken real interest in this effort. The goal is to have inexpensive, simple, and safe ways to prevent iron deficiency in infants and toddlers throughout the world.

The Interviewer: Dorian Friedman is the policy editor at *The American Prospect,* a monthly political magazine, and a former associate editor at *U.S. News & World Report*. She is based in Washington, D.C.