

### Exacerbation of infectious diseases by iron supplementation

Dear Editor,

Lima et al. investigated the impact of weekly treatment with ferrous sulfate on hemoglobin level, morbidity and nutritional status of anemic infants.<sup>1</sup> With regard to morbidity, they found that lower Hb levels were associated with greater duration of diarrhea. Because of the development of anemia in children not on iron supplements in their study cohort, the authors suggested preventive iron supplementation. The authors also suggest that patients with iron deficiency have a higher prevalence of infections due to the adverse effects of iron deficiency on the immune system. These assumptions by the authors cannot be justified on the basis of current evidence. A meta-analysis of 28 randomized controlled trials of iron supplements revealed a higher risk of diarrhea (incidence rate ratio: 1.11; 95%CI 1.01-1.23;  $p = 0.04$ ) in people who received iron compared to those given placebo.<sup>2</sup> In infants in Bangladesh, iron supplementation resulted in a 49% increase ( $p = 0.03$ ) in the number of episodes of dysentery.<sup>2</sup> More important are the findings of the largest study on iron supplementation in children so far including 24,076 children (with and without anemia) in Pemba (Tanzania).<sup>3</sup>

This randomized, placebo-controlled trial had to be terminated early because children who received iron supplements were 12% (95%CI 2-23;  $p = 0.02$ ) more likely to die or needed hospital treatment. This was partly due to a significantly increased risk of malaria-related complications. Independently, there was also an increase risk of serious adverse events, deaths and admissions to hospital due to other infectious diseases including pneumonia, sepsis, meningitis, measles and pertussis. Only the subgroup of children with anemia had some benefit that resulted in fewer hospital admissions or deaths, and children with iron deficiency without anemia were not adversely affected. A review by Oppenheimer<sup>4</sup> including controlled trials of iron supplementation in all age groups concluded that iron supplementation increased episodes of clinical malaria in six of seven trials.

The mechanisms by which iron can exacerbate infectious diseases are well described and relate to *Plasmodium falciparum* infection due to the fact that iron inhibits the expression of inducible nitric oxide synthase, which subsequently down-regulates the formation of nitric oxide in macrophages. Nitric oxide is a critical element in macrophage-mediated antiplasmodial antibody-mediated cellular inhibition, which is the key element of immunity against blood stages of *P. falciparum*.<sup>5</sup> Iron is also essential for multiplication of bacteria, including *Escherichia coli*, *Mycobacteria* sp, *Shigella* sp and *Staphylococcus* sp.

On the basis of these data a general recommendation of iron supplementation for all children in a population with a high prevalence of iron deficiency anemia and infectious diseases is not justifiable. Only children with proven iron deficiency anemia have been shown to benefit from iron supplementation. If children without iron deficiency are given iron supplements they may not only suffer from more severe complications of infectious disease, but also have impaired growth.<sup>6</sup>

#### References

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doi:10.2223/JPED.1592

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#### Author's reply

Dear Editor,

The issues addressed in the letter to the editor written by Dr. Michael Eisenhut are included into the list of scientific issues dealt with in the literature on anemia, which has triggered the search for new drug therapies, as well as for other control strategies.

Dr. Eisenhut's concern about the association between iron supplementation and an increase in infectious processes, in populations in which iron deficiency has not been confirmed, is quite pertinent. In countries such as Brazil, in areas where malaria is nonendemic, anemia affects over two thirds of the infant population aged 6 to 24 months, and most cases of

anemia diagnosed by the measurement of hemoglobin levels ( $< 11$  g/dL), according to the World Health Organization (WHO),<sup>1</sup> result from iron deficiency. Therefore, the Brazilian Ministry of Health recommends weekly iron supplementation for this risk group. The recommendation of one weekly dose is an attempt to minimize side effects, such as diarrhea, and to increase mothers' treatment adherence.<sup>2</sup>

Our results show a longer duration of diarrhea related to the severity of anemia, and also show that the groups of children with and without anemia submitted to the intervention had similar morbidity rates after treatment. The lack of a placebo-controlled group does not allow us to confirm the effect of iron supplementation. Supposedly, the decrease in morbidity caused by diarrhea in anemic children at the end of treatment might be a consequence of iron supplementation in children with iron deficiency.<sup>2</sup>

Other relevant issues related to public health interventions include sickle cell anemia, mainly in regions where de-

scendants of African immigrants abound in large numbers, and this has sparked off political and scientific debates among academics, technicians and community members, urging them to ponder over a solution to the problem.

### References

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