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Iron and folate supplementation: an effective intervention in adolescent females[1,2]

Mary Frances Picciano

Micronutrient deficiencies affect ≈2 billion people worldwide, or roughly one-third of the human race. Adverse consequences can be profound. As a result of micronutrient deficiencies, a large portion of the world's population is placed at risk of disease, disability, and even death (1). The most prevalent micronutrient deficiency is iron deficiency and segments of the population at greatest risk are children and women of childbearing age because of increased requirements for growth and reproduction. According to World Health Organization data, the prevalence of iron deficiency anemia in developing countries is 46–51% for children and 42% for women. Even in the United States, iron deficiency is still relatively common in toddlers, adolescent females, and women (2). Data from the third National Health and Nutrition Examination Survey (1988–1994) indicate prevalences of iron deficiency of 9% for toddlers aged 1–2 y and 9% and 11% for adolescent females and women, respectively (2).

In the past, most efforts directed at eliminating a micronutrient deficiency have focused on a single nutrient and results have not been wholly satisfactory. In this issue of the Journal, Tee et al (3) present their findings of a well-conceived and well-executed study in which they provided both iron and folate in their supplementation protocol for the elimination of iron deficiency among adolescent females in Malaysia. The results are fascinating. Hemoglobin and ferritin measurements were made at baseline and after 12 and 22 wk of weekly supplementation with either 60 or 120 mg Fe and 3.5 mg folate in adolescent females who had hemoglobin concentrations indicating mild anemia, borderline anemia, or no anemia. A subgroup of the adolescents with borderline anemia received folate supplementation alone. Mean hemoglobin concentrations increased significantly in all groups, but whereas ferritin increased in the iron-supplemented groups, it decreased in the group supplemented with folate alone. Further evaluation indicated that folate supplementation alone did not produce a hemoglobin response if initial ferritin concentrations were low. These findings underscore the importance of considering multiple micronutrient deficiencies in populations at risk of iron deficiency and anemia.

Maternal iron deficiency anemia is linked to premature uterine contractions during pregnancy, low birth weight, and maternal mortality. The extent to which concomitant folate deficiency is a contributing factor to poor pregnancy outcome associated with maternal iron deficiency has not been explored. Folate deficiency is often precipitated by reproduction because requirements are similarly high during pregnancy and lactation. The most recent recommended dietary allowances for folate of 600 and 500 μg/d during pregnancy and lactation, respectively, reflect that fact (4). Serum ferritin concentrations in the first trimester of pregnancy are useful in predicting the risk of developing iron deficiency later in pregnancy and normally decrease in the second and third trimesters, even in women taking iron supplements (5). Scholl (6) reported recently that high concentrations of ferritin (>41 μg/L) at week 28 of gestation, but not at entry to prenatal care (15.0 ± 4.9 wk gestation), increased the risk of preterm (31–36 wk gestation) and very preterm (24–30 wk gestation) delivery, but the risk changed if the concentration of ferritin declined from entry. If the concentration of ferritin declined as expected, a high ferritin concentration had no effect on outcome. Factors associated with failure of ferritin to decline were iron deficiency anemia in early pregnancy and low serum and red cell folate concentrations. It is tempting to speculate that a concomitant folate deficiency may have produced a functional iron deficiency by impairing cellular iron utilization when iron stores were sufficient.

Compliance with the supplementation protocol was excellent in the study reported by Tee et al (3). More than 96% of the adolescent females took 20 of the 22 supplements and the reported side effects were minimal (<2.2%). This high compliance rate was due in large part to the active participation of teachers, who verified that tablets were taken through direct observation most of the time. In a recent study conducted in Iran (7), pregnant women's compliance with taking iron supplements was assessed through direct interview and was controlled by using a direct measure for detecting iron in the stools. Eighty-one percent of women reported taking their iron supplements regularly, but only 21% of them had positive test results for stool iron. These findings suggest that compliance rates may be overestimated in many studies and stress the need to involve the entire community in the intervention strategy.

A particularly notable aspect of the study by Tee et al (3) was the inclusion of 2 doses of supplemental iron in their protocol. The hemoglobin and ferritin responses were similar regardless of the dose of supplemental iron. As pointed out by the authors, these

[1] From the Department of Nutrition, The Pennsylvania State University, University Park, and the Office of Dietary Supplements, National Institutes of Health, Bethesda, MD.

[2] Reprints not available. Address correspondence to MF Picciano, The Pennsylvania State University, Department of Nutrition, 126 Henderson Building South, University Park, PA 16802. E-mail: mfp4@psu.edu.

findings indicate that the lowest dose of iron used can effectively be used in future programs aimed at eradicating iron deficiency in the population studied. Iron supplementation has come under close scrutiny recently because redox-active forms of iron such as ferrous sulfate, which was used in the study by Tee et al (3), are known to catalyze free radical–mediated peroxidative reactions. Results of animal studies suggest that in iron deficiency the intestine is more susceptible to iron-mediated peroxidative damage and functional impairment after supplementation than in iron sufficiency (8). Diets high in iron also are reported to decrease the activity of manganese superoxide dismutase, the enzyme that functions in the mitochondria to detoxify superoxide radicals (9).

In summary, adolescent females represent a group at high risk of iron deficiency both in developing and industrialized countries of the world. The iron and folate intervention in Malaysia reported in this issue of the Journal was most effective and should serve as a prototype for future studies aimed at eliminating iron deficiency. Continued study is needed to determine the minimum effective dose of iron needed in such interventions and the possible involvement of other micronutrients—particularly folate—and factors that enhance compliance.

REFERENCES

1. Howson CP, Kennedy ET, Horwitz A, eds. Prevention of micronutrient deficiencies: tools for policymakers and public health workers. Washington, DC: National Academy Press, 1998.
2. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. JAMA 1997;277:973–6.
3. Tee E-S, Kandiah M, Awin N, et al. School-administered weekly iron-folate supplements improve hemoglobin and ferritin concentrations in Malaysian adolescent girls. Am J Clin Nutr 1999;69:1249–56.
4. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Daily reference intakes for thiamin, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press, 1998.
5. Bentley DP. Iron metabolism and anemia in pregnancy. Clin Hematol 1985;14:613–28.
6. Scholl TO. High third-trimester ferritin concentration: associations with very preterm delivery, infection, and maternal nutritional status. Obstet Gynecol 1998;92:161–6.
7. Bondarianzadeh D, Siassi F, Omidvar N, Golestan B, Keighobadi K. Low compliance with the iron supplementation program among pregnant women in the rural areas of Kerman District, I.R. Iran. Nutr Res 1998;18:945–52.
8. Srigiridhar K, Nair KM. Iron-deficient intestine is more susceptible to peroxidative damage during iron supplementation in rats. Free Radic Biol Med 1998;25:660–5.
9. Kuratko CN. Iron increases manganese superoxide dismutase activity in intestinal epithelial cells. Toxicol Lett 1999;104:151–8.