Improving the assessment of iron status\textsuperscript{1,2}

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Iron deficiency remains the most prevalent micronutrient deficiency worldwide. The consequences for affected individuals and the economic productivity of societies are substantial. Pregnancy (because of the risk of maternal death, preterm labor, low birth weight, and neonatal mortality) and early childhood (because of adverse effects on cognitive, motor, and emotional development that may only be partially reversible) are 2 parts of the human life cycle during which optimal iron nutrition is critically important (1).

Estimates of iron deficiency prevalence have been based on hemoglobin in most countries (2). Sensitivity is low because of the extensive overlap between the hemoglobin values of iron-deficient individuals and those who have adequate iron stores (3, 4). Poor specificity is an even greater limitation in countries where multiple nutritional deficiencies as well as malaria and other infections are common causes of anemia. A combination of laboratory measurements has been used to identify iron deficiency more accurately (5) and to estimate the size of body iron stores. However, these methods require as many as 5 different assays and use hemoglobin concentrations as the measure of the severity of iron deficiency. In 1990 Skikne et al (6) subjected 14 healthy adult volunteers to quantitative phlebotomy while measuring serial serum transferrin receptor and serum ferritin. They showed that body iron could be calculated from the serum transferrin receptor:serum ferritin ratio (R:F body iron). Two important advantages of this method are the ability to perform determinations on small capillary blood samples and the fact that it provides a continuum of values ranging from normal to tissue iron deficiency and iron deficiency anemia that are not dependent on hemoglobin concentrations. Furthermore, it is the first technique that has been calibrated against experimentally determined iron stores in healthy men and women, admittedly in a small number of subjects.

Validation by phlebotomy cannot be applied to children and pregnant women, groups who are at greatest risk of nutritional iron deficiency. Indirect evidence for the validity of the estimate in young children was reported in 2 studies. R:F body iron in Bolivian mothers and their children was highly correlated (7). Estimates for the prevalence of iron deficiency on the basis of R:F body iron were similar to those calculated by earlier methods in 3–5-\text{y-old} children in the United States (8). In this issue of the Journal, the study reported by Mei et al (9) provides comparable evidence for the validity of the approach in pregnancy. It is the first report describing iron status distribution in a representative sample of pregnant women in the United States. It shows that a substantial proportion of women are iron deficient in their second and third trimesters, especially if they are multiparous. There were significant ethnic differences. The prevalence of iron deficiency was highest among Mexican American and non-Hispanic black women.

Wider use of the R:F body iron estimate to characterize iron status in other segments of the population and in other countries should be encouraged. It is anticipated that the method will provide a much more accurate reflection of the true prevalence and severity of nutritional iron deficiency. It has been adopted for current and future National Health and Nutrition Examination Surveys (NHANES) in the United States. Every effort should be made to reduce the cost to make it available to resource poor countries where populations are at greatest risk of iron deficiency. The R:F body iron estimate also has proven utility as a sensitive measure of the impact of efficacy in iron fortification trials. It provides a quantitative estimate of the change in iron status. The bioavailability of the added iron can be derived from the change in iron status and the quantity of additional iron consumed during the trial.

The R:F body iron estimate is also an important research tool. The size of the iron store required at each stage of pregnancy to ensure an optimal outcome for the mother and the child (birth outcome and development during the first year) is unknown. Furthermore, whereas most women will require an iron supplement to ensure that the requirements of pregnancy are met, it has been postulated that iron supplementation of iron-sufficient women may increase the risk of oxidative damage and hemoconcentration. The observations reported by Mei et al (9) justify future research to correlate pregnancy iron status during each of the trimesters with pregnancy outcomes such as preterm birth, low birth weight, neonatal mortality, and infant development. It should be possible to define the optimal dose for iron supplements for pregnancy more precisely. Similar studies in children that correlate body iron with cognitive, motor, and emotional maturation will also be very important.

However, the R:F body iron estimate has several limitations. The most urgent may be the current availability of several commercial assays that yield different ranges of values. The Cook

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calculation can be used only if commutability with the assay used in that study is established. International reference standards are now available for both ferritin and transferrin receptor assays. There is a pressing need to calibrate transferrin receptor assays against this standard so that research observations correlating iron status with functional outcomes can be applied more generally. More research is needed to establish the suitability of the approach for populations in which infectious disorders are prevalent. The feasibility of correcting ferritin values for the effects of inflammation and transferrin receptor values for changes in erythropoietic rate needs to be addressed. Thalassemia carrier status may prove to be another confounding variable.

In conclusion, improved assessment of iron status will have an important effect on establishing the true worldwide prevalence of functionally significant iron deficiency as well as on the design and implementation of interventions to improve iron nutrition. However more work is needed to establish the utility of these estimates in the presence of infection and to make them available to populations in resource-poor regions where the risk of iron deficiency is greatest.

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REFERENCES