Iron Deficiency during Pregnancy: Blessing or Curse?

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(See the brief report by Kabyemela et al., on pages 163–6.)

Iron deficiency is the most common micronutrient deficiency and the most common cause of anemia among pregnant women worldwide [1]. Pregnancy may require as much as 1000 mg of elemental iron to meet the demands for maternal red blood cell expansion and fetal erythropoiesis and to account for blood lost at delivery [2]. As part of its standards for maternal and neonatal care, the World Health Organization recommends routine iron supplementation of 60 mg daily for pregnant women living in areas where malnutrition is prevalent [3]. The rationale underlying this policy is the observed association of anemia with adverse pregnancy outcomes. Specifically, anemia has been linked with low birth weight, preterm birth, decreased infant iron stores, and consequent impaired cognition and growth of the child [4–7]. For the mother, severe anemia may increase the risks of cardiac failure or death from peripartum hemorrhage [7, 8]. In a recent review of 40 trials involving >12,000 women, routine daily iron supplementation increased hemoglobin levels by ~7.5 g/dL and was associated with a decreased risk for anemia at term (relative risk, 0.56; 95% confidence interval, 0.40–0.78) for the 4 highest-quality studies [9].

In areas of the world where malnutrition is most prevalent, malaria is also of significant concern. Independent of the resultant anemia, malaria during pregnancy is linked with many of the same negative pregnancy outcomes as anemia. Low birth weight in particular may result from placental sequestration of Plasmodium falciparum–parasitized erythrocytes [10]. In this issue of the Journal, Kabyemela et al. [11] report an intriguing association between iron deficiency and a decreased risk for placental malaria, calling into question the wisdom of routine iron supplementation during pregnancy.

Over a 3-year period, 445 women were recruited into this cohort at the time of delivery in the Muheza district of northeastern Tanzania. Iron stores were assessed by measuring serum ferritin levels, with iron deficiency defined as levels of <30 ng/mL in the absence of inflammation (defined as a C-reactive protein level of ≤8.2 ng/mL) or <70 ng/mL in the presence of inflammation (defined as a C-reactive protein level of >8.2 ng/mL). Iron deficiency was quite common. Overall, 78% of the study group had inadequate iron stores, with an increased prevalence of iron deficiency (82%) among mothers who had been pregnant previously, compared with the prevalence (68%) among first-time mothers. Kabyemela and colleagues do not report the proportion of subjects that were anemic, nor do they report the proportion whose pregnancies resulted in low birth weight or preterm birth. However, the mean hemoglobin level was >11 g/dL for both the iron-deficient and the iron-replete groups, suggesting that the study population did not consist of severely anemic women, despite the frequency of iron deficiency.

In this study, iron deficiency appeared to afford protection against placental malaria, with an 80% reduction in the odds of infection for iron-deficient women. Results were most striking for primigravid and secundigravid women but did not quite reach statistical significance for multigravidae. The potential biological basis of this observation may be found in the basic requirement of iron for growth for most organisms [12]. Malaria parasites also require iron for synthesis of proteins, such as cytochromes and superoxide dismutase [13]. This need has been exploited in the use of iron chelators that inhibit parasite growth and are under investigation as a new class of antimalarials [14].

Iron supplementation has been provided to children at risk for iron-deficient anemia, to prevent infectious and developmental complications. However, iron supplementation has, in a number of clinical trials, been linked to increased malaria prevalence. A meta-analysis by Oppenheimer [15] found that, in 5 of 9 studies, oral receipt of iron was associated with an increased rate of malaria. Important factors that may alter the risk of adverse outcomes with iron supplemen-
tion include malaria endemicity, age, route, and frequency of iron supplementation and hemoglobinopathies.

Should routine iron supplementation during pregnancy be abandoned in areas where malaria is endemic? Despite evidence that iron supplementation decreases the risk of anemia, efficacy against the more relevant end points of low birth weight, preterm birth, puerperal infection, and maternal mortality has not been demonstrated [9]. The mild physiologic anemia associated with pregnancy may, in fact, be beneficial. Because the viscosity of maternal blood decreases and, in turn, the flow of placental blood increases during pregnancy, it has been suggested that maternal-fetal nutrient exchange is improved [16]. Provision of iron supplements to a nonanemic woman may increase the concentration of hemoglobin to a level (>130 g/L) that negatively impacts her pregnancy. In a prospective trial of Mexican women who were taking daily iron supplements, an elevated hemoglobin level was associated with an increased risk for both preterm birth and low birth weight [17]. Additionally, maternal adverse effects of oral iron ingestion are common and include unpleasant adverse gastrointestinal events, such as constipation, nausea, and vomiting, that sometimes limit compliance.

As suggested by Kabyemela and colleagues, further work is needed to elucidate the risk-benefit calculus associated with routine iron supplementation during pregnancy in areas where both malnutrition and malaria are common. A prospective study to examine the benefit and risks of iron supplementation for pregnant women in malaria-endemic areas is needed that takes into account cofactors identified from iron supplementation studies in children. Additionally, we should not lose sight of the efficacy of bed nets, vector reduction, and intermittent presumptive therapy to prevent placental malaria, and these standard approaches should be incorporated into clinical studies.

References


