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New evidence that iron supplementation during pregnancy improves birth weight: new scientific questions[1,2]

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Anemia is extremely common in pregnant women. It is particularly high in areas of the world that also have high rates of low birth weight (LBW). Although conventional wisdom suggests that poor maternal iron status may compromise fetal growth, iron deficiency and anemia have thus far not been included among the prominent causes of intrauterine growth retardation (1). Whether there is a causal link between maternal iron nutriture and birth weight was considered in a meta-analysis (2) and a systematic review (3). Both concluded that the evidence was insufficient to infer that iron supplementation during pregnancy increased birth weight. This conclusion arose in part because the available studies suffered from one or more design problems (3). In the article by Cogswell et al (4) in this issue of the Journal, the relation between iron supplementation during pregnancy and birth weight is addressed with a better design than that used in many of the studies reviewed.

The study by Cogswell et al was a randomized, double-blind clinical trial in which 146 and 129 women received supplementation with iron (30 mg/d) and placebo, respectively. The women received their treatment for ≈8 wk (from 20 to 28 wk of pregnancy) and received additional iron from 28 wk until delivery as deemed necessary on the basis of iron-status measures at 28 wk. In this experiment, all subjects were nonanemic and iron replete at the time they were randomly assigned to treatment. Iron supplementation had no significant effect on hemoglobin or ferritin concentrations or on the proportions of women who had anemia, low iron stores, or iron deficiency anemia at 28 wk. Mean birth weight in the placebo group was low for an American population, ie, only 3072 g, and there was a relatively high proportion of LBW (16.7%). The infants whose mothers received iron from enrollment to 28 wk of pregnancy were 206 g heavier than those whose mothers received placebo, in part because gestation lasted 0.6 wk longer in the former group of infants. There was no significant difference between the groups in the rate of preterm delivery. The rate of preterm LBW, but not the rate of term LBW, was significantly lower in the infants whose mothers received iron supplementation than in the infants whose mothers received placebo; the proportion of small-for-gestational age infants born to mothers in the iron-supplemented group was less than one-half the proportion born to mothers in the placebo group.

The results of this trial were unexpected. The effect on birth weight was relatively large, much larger than nearly all the effects reported in the iron-supplementation trials reviewed by Mohamed (2) and Rasmussen (3). More surprising still, the benefit to birth weight occurred without demonstrable improvement in maternal iron status.

The implicit biological model is that inadequate iron intake causes inadequate iron status and hemoglobin production, which in turn lead to iron deficiency anemia. It is peculiar that Cogswell et al found an improvement in birth weight without a corresponding benefit in the prevention of poor iron status at 28 wk of gestation; this finding suggests 2 possible explanations. One explanation is that the placenta and fetus competed effectively for the supplemental iron, so that maternal iron stores and hemoglobin were not significantly affected by the treatment. It follows that increased absorbed iron in mid pregnancy affects placental or fetal metabolism to facilitate fetal growth through pathways that do not involve maternal hemoglobin concentration. In the present study, iron treatment may have affected birth weight because initial maternal iron status was good enough that placental or fetal competition for iron could occur. When maternal iron status is poorer than that in the present study or when supplementation starts later in pregnancy than it did in the present study, the fetus may not compete as effectively. If confirmed by appropriate additional studies, these findings would indeed be a novel contribution. A second possible explanation for the peculiar result found by Cogswell et al is that the relatively small sample size provided an unstable estimate of the effect, which, by chance, was much greater than the true effect.

We would be inclined toward the second explanation were it not for the results of another recently published trial conducted by Christian et al (5) in rural Nepal. This study was a much larger, randomized, double-blind trial that included 5 treatment groups of ≈1000 women each. The women in the control group were given 1000 μg vitamin A/d. The women in the other groups received folic acid (400 μg/d); iron and folic acid (60 mg/d and 400 μg/d, respectively); iron, folic acid, and zinc (60 mg/d, 400 μg/d, and 30 mg/d, respectively); or multiple micronutrients (the same daily doses of iron and folic acid plus additional vitamins). These supplements were given from enrollment at 11–12 wk of pregnancy until delivery (ie, for ≈26 wk of treatment). Maternal nutritional status was poor [height, 150 cm; body mass index (in kg/m^2), 19], and as indicated by other research in this population (6), preintervention iron status was probably also poor. Compared with the infants of control mothers, whose mean birth weight was only 2587 g, the infants of mothers who received folic

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acid were 20 g lighter (no difference in LBW), those whose mothers received iron and folic acid were 37 g heavier (16% lower LBW), and those whose mothers received multiple micronutrients were 64 g heavier (14% lower LBW) when measured within 72 h after birth. These treatments had no significant effects on the proportions of infants who were small-for-gestational age or preterm. Although these increments in birth weight were not large, it is remarkable that micronutrients had any effect on fetal growth, given the women's generally poor nutritional condition.

Together, the findings from these 2 trials add materially to the literature on the relation between iron supplementation during pregnancy and birth weight. They also challenge our understanding of the basic biology that may underlie this relation. A distinguishing feature of both studies is that iron supplementation was begun earlier in pregnancy (11–20 wk) than it was in the studies that were reviewed recently (2, 3). Indeed, in the trial by Cogswell et al, the intervention occurred only until 28 wk; after that time, both groups of women received iron according to the recommended protocol on the basis of their iron status at the time.

Given the high prevalence of iron deficiency in pregnancy and the longstanding (but until now unproven) hypothesis that iron deficiency causes LBW, it is remarkable that there has been so little work on the biological pathways through which maternal iron status may affect fetal metabolism and growth. These 2 trials provide new motivation for biochemical and clinical nutritionists to elucidate the underlying biology.

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