

Effectiveness and strategies of iron supplementation during pregnancy¹⁻³

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ABSTRACT Iron deficiency continues to be one of the most prevalent single-nutrient deficiencies in the world. Interventions are often designed to prevent the decrease in hemoglobin concentration and the decline in iron stores associated with pregnancy. Although this is believed to be desirable for both the health of the mother and the well-being of the growing fetus, some scientists disagree. Enrichment and fortification of food items, and dietary changes resulting from education interventions, have met with some success in developed countries, but not often in the developing world. A therapeutic approach to iron supplementation, rather than a public health-based approach, is used throughout much of the world but suffers from real, or perceived, problems of compliance. Large doses of iron are most often prescribed and are associated with side effects and with increased oxidative damage. Alternatively, delayed-release preparations and intermittent oral iron supplementation lead to better overall compliance and alleviate side effects. Daily iron intervention provides more protection against a decline in the storage iron pool in pregnant women than does an intermittent schedule, but the latter is generally associated with fewer side effects, better compliance, and possibly a reduction in risk of oxidative damage. An improved cost-benefit ratio associated with a lower-dose oral iron supplement may prove to be quite positive in the future. Currently, no single approach may be universally acceptable, although a moderate iron dosage protocol will likely provide the most benefit to those who require supplemental iron. *Am J Clin Nutr* 2000;71(suppl):1288S-94S.

KEY WORDS Iron supplementation, iron deficiency anemia, iron status, pregnancy

THE PROBLEM

Iron deficiency continues to be the leading single-nutrient deficiency in the world, affecting the lives of >2 billion persons despite considerable efforts to decrease its prevalence for the past 3 decades (1, 2). Many of these affected individuals live in the developing world; intervention approaches that appear quite feasible in the United States or Europe are impractical in economically poorer settings (3). Primary focuses have been to increase the amount and bioavailability of iron in the diet (4-7), to control infections that contribute to iron losses from the body (8), and to improve economic, educational, and social conditions that contribute to the high prevalence of iron deficiency (9-11).

New diagnostic tools are being developed to increase the sensitivity and accuracy of iron deficiency detection in field settings with the hope that improved detection will produce more effective interventions (12, 13).

Nutritional iron deficiency is highest in population segments that are at peak rates of growth, namely, infants, young children, and pregnant women. Pregnancy is a time in which the risk for developing iron deficiency anemia is highest, because iron requirements are substantially greater than average absorbable iron intakes. Physiologic demands for iron increase from 0.8 to ≤ 7.5 mg absorbed Fe/d, although there is considerable debate about the exact upper limits of this increased iron demand in the third trimester of pregnancy (14, 15). Such demands result in a decline in iron stores during pregnancy and ultimately can produce iron-deficient erythropoiesis and anemia because a positive or even neutral iron balance is difficult to attain. The median need for iron in the second and third trimesters of pregnancy is calculated to be nearly 4.6 mg Fe/d, whereas the 90th percentile is 6.7 mg Fe/d (14). These calculations are based on the estimation that the median iron need during pregnancy is 840 mg, with a 90th percentile of 1210 mg. If the iron needs for 6 mo of lactation are considered, the median total iron requirement would be 1018 mg absorbed Fe. This calculation translates into an additional median need of 426 mg Fe for this 15-mo period.

The decline in iron status that normally accompanies pregnancy results in an increase in the efficiency of absorption of dietary or supplemental iron (16, 17). However, there is a significant discrepancy between these 2 reports regarding the magnitude of the increase in iron absorption. As a result, it is uncertain whether pregnant women can "naturally" attain a neutral iron balance without the need for supplemental iron. Some scientists argue that it is not possible to maintain the iron status of a pregnant woman with normal dietary practices and that iron prophylaxis is necessary (18). The worldwide anemia prevalence data suggest that normal dietary intakes of iron are insufficient to meet

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peak daily requirements for a significant proportion of pregnant women (19). In the industrialized world, estimates suggest that $\geq 30\%$ of pregnant women will have depleted iron stores by the end of pregnancy, and in some population groups (eg, adolescents) depleted iron stores could occur in $\geq 80\%$ of the population (19, 20). In the developing world, these estimates are higher. For example, 47% of pregnant women in Africa, 39% of pregnant women in Latin America, 80% of pregnant women in Southeast Asia, 65% of pregnant women in the eastern Mediterranean, and 40% of pregnant women in the West Pacific are believed to be anemic (21). Worldwide, at least one-half of anemia cases occurring during pregnancy are due to nutritional iron deficiency. Subclinical iron deficiency is nearly as widespread as iron deficiency anemia. Current control programs include supplementation, fortification, dietary modification, and parasitic disease control.

The problem therefore is as follows: how does a pregnant woman get the necessary amount of iron in her diet knowing that normal dietary practices are likely to be insufficient for a good portion of her pregnancy? Implicit questions regarding an iron intervention are numerous. 1) What are the endpoints to be considered for a successful intervention? Is the goal to prevent anemia or to prevent a decrease in plasma ferritin? Is the goal to optimize fetal growth and outcome, or is it to minimize maternal or fetal morbidity and mortality? 2) Are there potentially toxic side effects of overzealous iron administration during pregnancy? 3) Is it better to improve iron stores antenatally so that sufficient maternal iron is in place for the critical first trimester of pregnancy?

First, I will discuss the consequences of iron deficiency on the well-being of the mother and on the growth of the fetus have been reviewed by many scientists (15). Recent scientific reviews form the basis of current recommendations for nutritional iron status assessment and iron deficiency intervention through the provision of supplemental iron during pregnancy by the World Health Organization (22), the Life Sciences Research Office (23), and the National Academy of Sciences Institute of Medicine (24). The most recent of these, the 1993 Institute of Medicine recommendations, place new emphasis on the need to assess iron status during pregnancy before the blanket administration of iron supplements. The prevention of iron deficiency in pregnancy is desirable, because severe iron deficiency anemia (hemoglobin concentration of 90–100 g/L) in pregnancy is related to both impaired fetal and maternal health (15). At the anemia end of the hemoglobin distribution curve, birth weight is decreased, complications occur (eg, toxemia, labor and delivery complications, small-for-gestational age infants), and maternal functioning is impaired. However, a modest drop in hemoglobin concentration in pregnancy appears to be a normal physiologic event; hemoglobin concentrations reach a nadir in the mid second trimester of pregnancy and then rise again in the third trimester. Maternal hemoglobin distribution and infant outcomes have a U-shaped curve, with an increased risk for infants whose mothers have either a very low or a very high hemoglobin concentration (15, 25, 26). Thus, the prevention of severe anemia appears desirable. It is less obvious whether the prevention of a decline in serum ferritin during pregnancy is a necessary or desirable dependent variable. Few functional outcomes, for either mother or baby, are associated directly with depletion of iron stores alone; rather, the benefit derived is from an improvement in maternal and fetal iron stores (27–30). This can be a true long-term benefit for both mother and infant because the mother may enter her next pregnancy with better iron

reserves and the infant may be weaned with a larger iron store. An exception to this may be the neurologic development of the infant. Animal studies of perinatal and early postnatal iron deficiency clearly indicate that iron deficiency leads to alterations in brain iron content, distribution, and metabolism (31, 32). A recent report from the International Nutritional Anemia Consultative Group (33) summarizes the extensive human literature on the adverse effects of iron deficiency in early life on mental performance. This report observes that iron deficiency in early life is likely to have negative consequences for normal neural development and functioning.

The second major question posed in the preceding section is based on emerging knowledge that iron, in excess, is an active participant in the Fenton reaction, which results in the production of free radicals and oxidative damage (34, 35). High single doses of iron as a fortificant or as a dietary supplement may be associated with increased oxidative product formation and the initiation of various pathogenic processes such as cardiovascular disease, neuropathologies, and cancer (36–38). Thus, the implications of adding a large amount of fortificant iron to a food consumed predominantly by pregnant women, or the provision of a very large dose of supplemental oral iron, need to be reconsidered.

The third major question posed concerns the timing of maternal iron deficiency and the greatest negative effect of the deficiency on fetal growth. Strong evidence shows that iron deficiency in the first trimester of pregnancy results in significant decrements in fetal growth, whereas iron deficiency anemia in the second and third trimesters has little effect on fetal growth (26, 39). Most perinatal iron intervention programs rely on the initiation of treatment at the first visit of the newly pregnant woman to her health care provider, somewhere around 10–15 wk of pregnancy. It is possible, however, that by this time the real window of opportunity for a positive intervention against iron deficiency has passed if fetal growth and development are the dependent variables considered. Perhaps targeting intervention programs to the prenatal period may be of a greater benefit than relying on intervention in the late first trimester or early second trimester of pregnancy (20, 24).

INTERVENTION APPROACHES

Intervention approaches against iron deficiency have taken both public health and clinical or therapeutic tacks. As described by Viteri (14), many studies concerning iron intervention in pregnancy have examined efficacy (ie, biological effectiveness) with a variety of outcome measures. The public health approaches of education and iron fortification have had great success in the United States in reducing the prevalence of anemia in women of reproductive age and in young, growing infants (20, 24). Programs targeted to increase the consumption of iron-fortified and iron-enriched products consumed by lactating women and young infants have reduced the prevalence of iron deficiency in these 2 sections of the population (24). Fortification of baby foods has resulted in a dramatic reduction in childhood iron deficiency in much of the United States (20). New fortification products incorporating chelated iron continue to be developed and are used in developing countries in an attempt to improve countrywide iron status (40, 41). The number and variety of these products has grown tremendously in the Western world; fortificant iron likely constitutes close to 50% of the iron intake in some segments of the population.

A variation on the theme of food fortification is the emerging field of designer foods in which particular components of a food item are either increased or decreased through biomanipulations. Such attempts to increase bioavailable micronutrients include genetically deleting iron absorption inhibitors (ie, removal of phytic acid from maize and beans), and genetically enhancing the amount of nutrient a plant source can provide (ie, over-expression of a plant's production or incorporation of a micronutrient in the plant's structure) (41).

The clinical or therapeutic approach to preventing iron deficiency focuses on the rapid restoration of reduced iron stores through direct interventions that supplement iron consumption by the individual. This is primarily accomplished through the provision of oral iron supplements. Oral iron supplements are effective at reducing the prevalence of anemia and improving the iron status of compliant individuals and populations (17, 20, 27, 42, 43), but run the risk of providing more iron than what is ideal when consumed by individuals who are not iron deficient. The estimated prevalence of anemia in some populations of pregnant women, however, does not improve after consumption of iron supplements (44, 45). Although some investigators conclude this is because of low compliance and side effects (46), others report that poor compliance is unrelated to side effects (47, 48).

A significant change in the approach to oral iron supplementation is occurring with the suggestion that lower-dose iron supplements be provided less frequently. That is, a new balance is being sought between providing too much iron and not enough iron. The need for ≈ 1 mg additional Fe/d during pregnancy was often treated with 60, 120, or even 180 mg Fe/d as the supplement dose. If mean absorption of iron is assumed to be 5% (a low estimate given the published data on the absorption of ferrous sulfate in iron-depleted subjects), then 3, 6, and 9 mg of absorbed Fe are derived from these commonly used doses. Early in pregnancy, the smallest dose of supplemented iron is likely to be 5 or 6 times the additional iron need, whereas later in pregnancy, the smallest dose of iron is 3 times the additional iron need. This assumes no change in iron absorption efficiency, which is an unlikely event (16, 17). However, the iron needs of some individuals during pregnancy are substantially above, or below, this median estimate of need (20). Iron supplement use in the United States is estimated at 83% during pregnancy with compliance of ≥ 3 times/wk for 3 mo (48). There is a clear increase in reported side effects with increasing supplement dose of iron (49, 50).

Intravenous iron preparations are a therapeutic mainstay for severely iron-deficient individuals when they are unable to take oral preparations (51). In one study, administration of oral ferrous sulfate (60 mg Fe) was compared with an intravenous iron-sucrose complex (52). Patients randomly assigned to the ferrous sulfate group experienced considerable side effects; 6% of patients could not tolerate the medication, 30% of patients experienced gastrointestinal distress, and 30% of patients were poor in compliance. The intravenous iron-treatment group reported no side effects and had a more significant hemoglobin response in a shorter period of time than those patients in the oral iron group. Similar results were reported in patients receiving intravenous iron polymaltose compared with patients receiving oral iron fumarate (53).

Iron supplementation has traditionally been a therapeutic approach initiated after the diagnosis of iron deficiency (54). The efficacy of the supplement intervention is dependent on 1) the composition of the diet, 2) the presence of a physiologic or patho-

logic condition that would alter iron absorption or loss, 3) the composition of the supplement, 4) the severity of the iron deficiency at baseline, and 5) the duration of the intervention. Many of these issues have been addressed during pregnancy. The composition of the diet and its aggregate of inhibitors and enhancers of absorption establish the baseline for daily iron absorption and also the gastrointestinal environment from which the iron compound will be absorbed. A pathologic disease state or a certain physiologic state (eg, achlorhydria) could, however, dramatically alter iron balance and the efficacy of the supplement. The composition and dose of the supplement have been examined in many countries and in many settings in an attempt to optimize absorbable iron. An ongoing, active scientific discussion is centered around the efficacy of daily oral iron supplementation compared with intermittent iron supplementation (55, 56). Traditional daily iron supplementation is based on the therapeutic approach of using a high-dose iron salt or elixir that provides between 60 and 180 mg Fe/d. Much of this high dose of iron can enter the mucosal cell through effects of mass action as well as through well controlled, normal absorptive routes (38, 57). Studies of iron absorption in which protocols simulated the intermittent dosing protocol provide evidence that there is increased efficiency of absorption when animals are tested (58–60), and a modest or no benefit when subjects are human (55, 61, 62).

The 1990 Institute of Medicine Committee and the 1991 Life Sciences Research Office guidelines recommended that nonanemic women consume 30 mg Fe/d beginning in the 12th week of pregnancy, and that iron be taken between meals, but not with coffee or tea (20, 24). If anemia is present and a low plasma ferritin concentrations confirms iron deficiency, the daily dose of iron should be 120 or 180 mg Fe/d. The 1993 Institute of Medicine report (24) recommended that women be screened for anemia at the first obstetric clinic visit, and that clinicians prescribe 30 mg Fe/d if the woman is anemic (hemoglobin concentration of 109 g/L) and iron deficient (ferritin < 30 $\mu\text{g/L}$). If ferritin concentrations are < 12 $\mu\text{g/L}$, then it is recommended that higher doses of iron be consumed. If there is an indication of a marginal iron reserve (ie, ferritin > 30 $\mu\text{g/L}$), then no iron intervention is appropriate at this time. These recommendations attempted to establish guidelines that would help to avoid blanket iron intervention during pregnancy. Higher iron doses are frequently associated with side effects, including gastrointestinal upset, constipation, and nausea. Slow-release iron preparations and alternative, gastric delivery systems provide substantial relief from these side effects while still providing the desired therapeutic amounts of iron (63). Note that higher doses of iron often do not provide any greater benefit to the pregnant woman with regard to correction of anemia (20). The Food and Agriculture Organization/World Health Organization calculated iron requirements for pregnant women based on the need for increased absorbable iron and the need for increased heme iron in the diet (22). The World Health Organization also advocated supplementation of 60 mg Fe/d along with 250 μg folate (1, 22, 23).

Several questions raised by the Institute of Medicine Committee of 1993 have yet to be entirely resolved (24). For example, are there adverse outcomes associated with routine iron supplementation (14)? The assumption by the Institute of Medicine Committee was that adverse outcomes associated with elevated hemoglobin late in pregnancy are unrelated to iron status but rather are related to fluid homeostasis. A study from South Africa determined that there was no benefit, in terms of fetal outcome, of

withholding iron supplementation (18). Thus, the question becomes, Does extra iron provide a benefit or does it do harm? Such points are discussed in greater detail within this issue (64).

A second significant point of discussion is whether routine iron supplementation produces a greater change in the iron status of pregnant women who are the most iron deficient, or whether all expectant mothers derive an equal benefit from supplementation. That is, should there be routine iron supplementation of all pregnant women? Existing data indicate that severely iron-deficient individuals are more efficient in absorbing iron and hence would derive more of a benefit from iron supplementation than less iron-deficient individuals (4–7). A related question concerns the dosage of iron administered to anemic subjects compared with that administered to subjects with iron-deficient tissues. One study showed that a smaller dose of oral iron can reduce the prevalence of anemia as effectively as higher doses, but that larger doses are necessary to significantly increase plasma ferritin (65). Milman et al (66) reported that iron (66 mg Fe/d) supplemented in the second trimester of pregnancy attenuated the elevation in erythropoietin in the third trimester. Combination heme- and nonheme-iron supplements at a dose of <20 mg Fe were effective at reducing the prevalence of low ferritin concentrations in pregnant women (67). A placebo-controlled trial in Norway involved \approx 90 women who were randomly assigned to either take a placebo, 27 mg elemental Fe with ascorbic acid, or 27 mg of a product containing both heme and nonheme iron (68). These low doses of iron in both treatment groups reduced the prevalence of low ferritin concentrations and anemia. The heme iron group actually improved in iron status from mid pregnancy to term, thus demonstrating the benefit of heme over nonheme iron for therapy. An attempt to reduce supplemental iron to an even lower dose, 18 mg Fe/d, in young nulliparous women during their first pregnancy met with negative results (45). Much greater doses of iron (100 mg Fe/d) were associated with higher Apgar scores and greater birth lengths of infants born to supplemented women compared with placebo-treated women in another study (69). Considering changes in maternal hematologic status only, there is no advantage of iron doses >60 mg/d (70) and perhaps no advantage of doses >30 mg/d (24). The number of side effects increases dramatically when the dose of iron increases. In an Indian study, 32%, 40%, and 72% of women experienced side effects as the iron dose rose from 60 to 120 to 240 mg Fe/d (70), respectively. Thus, dose and composition of the iron supplement clearly affect maternal outcome and may provide an alternative to the therapeutic high-dose approach.

Another alternative to high therapeutic doses of iron is to provide a delayed-release form of oral iron that would produce fewer side effects but still provide the iron necessary to meet physiologic needs (63). In such formulations, iron is released at a slower rate because of the action of gastric acid on the matrix containing the ferrous sulfate, thus reducing the bolus load of iron into the gastrointestinal system.

There is a growing sentiment among some investigators, especially in Third World countries where the prevalence of iron deficiency anemia during pregnancy is nearly 80%, that daily iron supplementation is ineffective (71–73). That is, compliance is low in many daily supplementation programs and there is a strong need to improve the coverage of at-risk populations when human and financial resources are limited. The question of compliance was examined in Tanzania where women in the 21–26th wk of gestation were given either 120 mg Fe or 50 mg of a gastric deliv-

ery system (delayed-release GDS) iron supplement daily for 12 wk (74). Adherence to iron supplementation was 42% in the 120 mg Fe/d group and 61% in the GDS preparation group. It is believed that both groups were compliant because of fewer experienced side effects. In addition, both iron dosages were considerably higher than what is reasonably required as treatment of iron deficiency in pregnancy. The authors suggest that 25% of what is considered to be a normal iron dosage would be more appropriate in this population.

The requirements of a successful iron supplementation program have been well described by others. Many significant actions must occur before the actual issues of compliance and success or failure of a supplementation program can occur. These include financial and infrastructure commitments, training of personnel, targeting of at-risk groups, quality control of the iron supplement and delivery system, and assessment of compliance. Schultink et al (73) studied compliance in a daily iron supplement program in the early 1990s and showed that as few as 36% of pregnant women were compliant even when they knew that the issue of iron supplementation was being studied. The authors concluded that coverage of the at-risk population was also quite low and that the need existed for a new approach to iron supplementation. As with all previous intervention approaches, a set of performance standards was established to determine the efficacy of the approach. That is, does intermittent oral iron supplementation work? Does it work well? Does it work for those who are severely anemic? Will compliance improve and is it economically viable in many developing countries? There are no clear answers for all of these queries, but many field trials have already provided data supporting the claim that intermittent iron supplementation can be as effective as daily iron supplements. The pros and cons of intermittent compared with daily iron supplementation have been reviewed in the biomedical literature (75–78). There are numerous complete research reports on randomized clinical intervention studies from around the world (79–85). Concerns regarding research design, iron dosage, and duration of intervention exist. Some studies used placebo intervention controls, whereas others did not, thus obscuring the strength of some of the studies. Nonetheless, a large number of individuals (including young children, older children, adolescents, and pregnant and nonpregnant women) with differing cultural food patterns have been studied to date. Most pertinent to the theme of this review are the clinical trials regarding interventions in pregnancy.


In a study with a loosely controlled design that included interventions for variable periods of time, Ridwan et al (83) examined 120 mg Fe as ferrous sulfate given weekly compared with 60 mg Fe given daily in women during the second and third trimesters of pregnancy. The intervention interval was between 8 and 20 wk, with all interventions starting at the first prenatal clinic visit and concluding at the 30th week of pregnancy. Initial and final hemoglobin concentrations in the 68 women supplemented daily with iron that were not significantly different from the hemoglobin concentrations of the 71 women supplemented weekly. However, the weekly dose of iron was insufficient to keep serum ferritin from decreasing slightly. The anemic women in both treatment groups responded equally to supplementation, thus showing no particular benefit of daily iron supplementation. A more tightly controlled study from China provided either a weekly iron supplement or a daily iron supplement to primiparous mothers and included a placebo control group (85). Sixty mg Fe as ferrous sulfate plus 250 μ g folate were given daily or

twice daily or 120 mg Fe was given weekly starting at the first prenatal visit at \approx 13–20 wk of pregnancy. Women were stratified to all treatment groups initially so there were no baseline differences in either ferritin or hemoglobin. The percentage of women who were anemic at the time of birth was not significantly different in any of the 3 iron-supplemented groups (18–28%) and was much less than the percentage of anemic women in the placebo control group (53%). Protection of maternal iron stores, as indicated by plasma ferritin, was also equivalent in the iron treatment groups.

Supplementation trials in pregnant women that included intermittent dosing schedule were also performed in Guatemala (86). Sixty milligrams of elemental Fe daily or 180 mg Fe weekly was provided to women in both a supervised and an unsupervised fashion. Sixteen percent of women who received daily iron supplements and 25% of women who received weekly iron supplements were anemic at term. A pseudo-control group of women who received the “usual care” of advisement to take oral iron supplements daily had a 33% prevalence of anemia at term. Six to eight times more side effects were reported by women taking iron supplements daily than by those taking iron supplements weekly. The effectiveness of the iron intervention was greater for the daily intervention group when rise in hemoglobin (13.1 compared with 9.6 g/L) was considered as the dependent variable. The biological significance of this is not clear. Plasma ferritin did not differ significantly between the daily and weekly intervention groups, a result seen in other intermittent dosing trials.

Several commentaries question the efficacy of the intermittent dosing schedule during pregnancy, stating that if compliance is poor with daily iron supplementation, it will be even worse with an intermittent trial (87, 88). This, of course, is a very real concern that needs to be addressed in future studies because a controlled setting was used for most of the intervention trials reviewed here. In addition, other dependent variables indicating the success or failure, or appropriate fetal growth and development measures need to be incorporated. Viteri (14) raises an important point with regard to the approach of intermittent iron supplementation in his review. If pregnancy is viewed as part of the reproductive cycle, then the more appropriate time for intervention is before pregnancy, not during pregnancy. With this viewpoint, the low-dose intermittent iron supplementation route becomes more attractive because the potential pitfalls of poor iron status in the first trimester of pregnancy may be avoided. The efficacy of this approach has yet to be determined.

It is important to return to many of the key unanswered questions raised by the 1993 Institute of Medicine report and a recent review of unresolved issues in iron interventions in pregnancy (24). 1) Is there a need for supplemental iron during pregnancy? That is, is there a benefit to the mother and the infant? In addition, who will benefit the most from iron supplementation: only the most anemic mothers and their infants, or will all pregnant women of low iron status derive some benefit from supplementation? 2) What approach will provide the most efficacious outcome? 3) If iron supplementation is provided, what dosage and schedule are the most beneficial? 4) Given the new knowledge regarding the relation of infant iron status to neurologic development, is there a clear imperative to prevent iron deficiency in newborns and thus avoid irreversible functional damage? 5) Is there a real health risk of too much iron? The blanket provision of therapeutic doses of iron, even during pregnancy, has come under close scrutiny because excess iron may be implicated in the pathogenesis of sev-

eral chronic diseases. The answers to these questions are largely unavailable at this time, but do warrant careful examination in the future because global estimates of the prevalence of iron deficiency anemia during pregnancy have not decreased in the past 2 decades, and many millions of women are affected. 

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