

Weekly iron intervention: the case for intermittent iron supplementation^{1,2}

John L Beard

The prevalence of iron deficiency anemia remains high in many parts of the world despite substantial efforts to alleviate this nutritional disease. The social, health, and economic costs of iron deficiency anemia are not insignificant and should always be considered, along with the clinical implications, in the broader context of public health concerns. Numerous published studies provide evidence of diminished worker productivity (1, 2), decreased physical performance (3), altered mental functioning (4, 5), delayed mental development (6–8), poor pregnancy outcomes (9, 10), and slowed growth in young children (11). Iron fortification programs to alter the basal consumption of iron and targeted interventions to decrease the intake of known inhibitors of iron absorption are viable alternatives to supplementation programs in some cases and need to be considered carefully. Iron supplementation is suggested when fortification programs or other food-based programs fail to reach the at-risk segments of the population. One of the oldest intervention routes has been the provision of daily oral iron supplements. This has been especially attractive to clinicians, for whom therapeutic treatments dominate the philosophy of intervention.

A debate has developed in the past 5 y regarding the desirability of intermittent iron supplementation compared with daily iron supplements. The primary proponents of the intermittent approach have a historical view based on their, and others, frustrations with the lack of effectiveness of daily iron intervention in developing countries (12–14). That is, compliance is low with 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 (12). 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, success, or failure are realized. These include financial and infrastructure commitments, training of personnel, targeting of at-risk groups, quality control of the iron supplement and delivery, and assessment of compliance. Schultink et al (15) studied compliance with 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 this issue was being studied. The authors concluded that coverage of the at-risk population was also quite low and the need existed for a new approach.

My perspective on this debatable issue is derived from a request from the Program Committee of the International Union of Nutritional Sciences Annual Meeting to argue one side of the

issue in an Oxford style debate format. My evaluation of this issue is based on several points: Does intermittent oral iron supplementation work? Does it work well? Does it work for those who are severely anemic? Can it work in a preventative fashion? and Will compliance improve? There are no clear answers to these queries. Several field trials have been completed and report data supporting the claim that intermittent iron supplementation can be as effective as daily iron supplementation.

The theory behind intermittent oral iron supplementation was based initially on the concept of a “mucosal block” of iron absorption (16). This theory argues that mucosal enterocytes down-regulate iron absorption in response to daily exposure to a high intake of iron. There is an increase in mucosal ferritin synthesis, an increase in the proportion of enterocyte iron that is stored in the cell, and a decrease in transfer of iron to transferrin in the vascular pool. Rodent studies by Wright and Southon (17) and Viteri et al (18) appear to confirm a more efficient uptake of iron with spaced or intermittent administration of iron supplements. Experimental evidence from controlled laboratory studies, argued by Hallberg in this issue of the *Journal* (19), do not support this claim of a functional mucosal block of iron absorption. Much of what we know and understand about iron bioavailability has been derived from that methodologic approach. But, we should all remember that according to aerodynamic theory, the bumblebee cannot fly. In empirical reality, we see them buzzing above the flowers. Hence, the argument that there is no differential absorptive benefit from spacing the oral iron doses “in theory” must confront the practical realities of the empirical demonstration. I examined objectively the published research regarding this issue and my opinions are based on the predominance of the evidence available at this time.

This is not the first review of published scientific literature on this topic (13, 20–23). Several full-length research reports on randomized clinical intervention field trials from around the world can be found in the published literature (24–30). These reports come from research groups centered in China (30); Jakarta, Indonesia (26–31); and Bolivia (25) (**Table 1**). Several other field trials have been completed, but are not yet published

¹From the Nutrition Department, The Pennsylvania State University, University Park.

²Reprints not available. Address correspondence to JL Beard, Nutrition Department, The Pennsylvania State University, University Park, PA 16802. E-mail: ITS@psu.edu.

TABLE 1

Country and reference	Subjects and design	Sample size ¹	Iron dosage	Duration of study	Key outcome variables ²	Significance of treatment effects
Indonesia (27)	2–5-y-old children: daily or twice-weekly treatments	44/group	30 mg Fe	8 wk	Hemoglobin responses	NS (difference between groups); $P < 0.001$ compared with baseline
Indonesia (26)	2–5-y-old children: weekly or placebo treatments	100/group	30 mg Fe	9 wk	Hemoglobin responses	$P < 0.001$ in Fe treatment compared with placebo, baseline
Bolivia (25)	3.5–8.2-y-old children: weekly, 5 times weekly, or placebo treatments	59/group	3–4 mg Fe/kg body wt	16 wk	Hemoglobin responses	NS (difference between 2 treatment groups); $P < 0.001$ compared with placebo (baseline)
China (30)	3–6-y-old children: daily, weekly, or twice-weekly treatment	80/group (30 anemic, 50 control)	6 mg Fe/kg body wt	12 wk	Hemoglobin responses; side effects	NS (difference between groups in hemoglobin response); $P < 0.001$ compared with baseline; $P < 0.05$ difference in side effects
Indonesia (28)	Pregnant women in 8–24 wk gestation: daily or weekly treatment	68 (daily treatment) and 71 (weekly treatment)	60 mg Fe/d or 120 mg Fe/wk	8–20 wk	Hemoglobin and ferritin responses; compliance	$P < 0.001$ for hemoglobin response compared with baseline; $P < 0.05$ for treatment differences in ferritin
Indonesia (29)	8–16-y-old girls: weekly iron + folate, or iron + folate + vitamins A and C	42/group	60 mg Fe	5 wk	Hemoglobin responses	NS (difference between groups in hemoglobin response); $P < 0.001$ compared with baseline

¹Group sizes are approximate because actual numbers of subjects varied slightly from this average or target.

²Hemoglobin response was calculated as the change from the baseline.

in peer-reviewed scientific journals and were not considered in this review. The commentaries referred to above (13, 20–23) have already critiqued the strengths and weaknesses of both sides of the debate and the concerns cited involve research design, dosage, duration of intervention, and other specific points for the field trials. In addition, there are concerns about the laboratory studies regarding small sample sizes, limited replication, and interpretation of single-meal radioiron absorption data. Some of the studies used placebo intervention control groups, whereas others did not, thus obscuring the strength of some of the conclusions. Nonetheless, a large number of individuals across a wide age range and cultural food patterns have been enrolled in field trials to date. If the report by Gross et al (24) published in 1994 in *The Lancet* is included in this list, the at-risk groups studied include preschool children, juveniles, adolescents, and pregnant and nonpregnant women. Each of these groups will be considered in the next several sections.

The 1995 study from Indonesia used a randomized, double-blinded trial of daily compared with twice-weekly ferrous sulfate (30 mg) given as a glucose syrup for 2 mo to 2–5-y-old children with iron deficiency anemia (27). The results of this brief therapeutic trial were that daily and twice-weekly iron supplements worked equally well regardless of the severity of anemia. The lack of a placebo intervention group, however, limits the scientific enthusiasm for this outcome. A second study from China also investigated young children and the potential effect of intermittent compared with daily iron supplements (30). This 3-mo therapeutic trial was of 3–6-y-old children given 6 mg FeSO₄/kg body wt daily, twice weekly, or weekly. The hemoglobin responses were similar in all groups, including both anemic and nonanemic children, although the group given the supplement daily had a substantially larger rise in serum ferritin than did the intermittently supplemented groups. Importantly, the reports of side effects were related to the frequency of iron supplementation, with many fewer side effects in the intermittently supplemented groups than in the group given the supplement daily. Again, the lack of a placebo intervention group limits the enthu-

siasm of some scientists for this study as well. A regression-toward-the-mean phenomenon is always a concern, although it is not a common observation for anemic children to suddenly achieve normal hemoglobin concentrations after iron supplementation for such short time periods as in both of these studies without some programmed form of intervention.

The mean rise in hemoglobin concentration in all treated children was greater than the normal daily variation of $\approx 4\%$. A more recent study regarding the effectiveness of intermittent iron supplementation in young children included a placebo intervention group but did not have a group that received the supplement daily (26). In this 9-wk study, 2–5-y-old children were given, weekly, 1 of 3 treatments: 30 mg Fe orally in syrup form, 30 mg Fe orally in syrup form plus an anthelmintic drug, or a placebo. The inclusion of a placebo group in this study provides some perspective on the interpretation of the 2 studies in young children mentioned previously. Although the children in the placebo group showed no significant rise in hemoglobin concentration over the intervention period, the prevalence of anemia in both of the weekly intervention groups fell dramatically and significantly. Thus, although no direct comparison with daily iron supplementation was possible, the effectiveness of intermittent oral iron therapy was shown relative to a placebo comparison group. An additional intervention trial including a placebo group, but performed in slightly older children from Bolivia, was published in 1997 (25). This study compared dosages of 3–4 mg Fe/kg body wt given 5 times weekly or once weekly to young children for 16 wk with that of a placebo group that received no supplement. The once-weekly dose reflected an attempt to examine the effectiveness of smaller than therapeutic doses of iron for long periods of time and proved as effective as the 5-times-weekly dosing strategy in promoting an elevation in hemoglobin concentrations. The placebo group again showed no significant change in hemoglobin concentration or prevalence of anemia over the 16 wk of the study.


Perhaps the greatest thematic concern voiced in many of the previous commentaries regarding weekly compared with daily

iron supplementation was the effectiveness of intermittent iron supplementation during pregnancy. The argument is made that it is impossible for intermittent iron supplementation to provide sufficient exogenous iron to meet the additional iron needs associated with pregnancy despite the rise in absorption efficiency during pregnancy. An at-risk group of pregnant women was studied in a loosely controlled design by Ridwan et al (28). Subjects were enrolled for various lengths of time and randomly assigned to receive 120 mg Fe as ferrous sulfate weekly or 60 mg Fe daily during their second and third trimesters. The intervention interval was between 8 and 20 wk, with all interventions starting at the first prenatal clinic visit and concluding at 30 wk of pregnancy. The 68 women supplemented daily had initial and final hemoglobin concentrations similar to those of the 71 women supplemented weekly. The weekly dose of iron was insufficient to keep serum ferritin from falling slightly. The women in both treatment groups who were anemic responded equally to the therapy, thus showing no particular benefit of the daily iron supplementation.

Although laboratory tests and field trials both need to be held to rigorous scientific standards, the real world issues of insufficient resources or programs to significantly diminish the worldwide prevalence of iron deficiency anemia still face the international community. In the clinical intervention studies reviewed in this debate, nearly 1000 subjects participated. The groups receiving intermittent iron supplementation achieved significant benefits in all trials regardless of age, culture, or research group. That is, the prevalence of anemia was diminished in these groups and they experienced a benefit that was equal to that of the groups supplemented daily. In some of these studies, side effects diminished and compliance improved in the intermittently supplemented groups.

New approaches need to be developed that address the needs of at-risk groups that improve compliance, that have fewer side effects, and that simplify the logistics of either curing or preventing iron deficiency (32). Blanket provision of therapeutic doses of iron, even during pregnancy, has come under closer scrutiny (33) because excess iron may be implicated in the pathogenesis of several chronic diseases (33; see Appendix). Thus, the provision of large doses of iron may be deleterious in some circumstances because of the generation of oxy-free radicals (34). Discrete studies of oxidative damage in relation to iron supplementation given weekly compared with daily are likely ongoing in several laboratories and the results will be interesting. The potential negative consequences of daily, high intakes of iron, however, need to be recognized.

In conclusion, as an "uninvested" reviewer of the published literature, I would like to comment on the initial set of evaluation criterion. I believe that in controlled situations, intermittent iron supplementation can effectively reduce the prevalence of iron deficiency in several risk groups. As to whether it works well or not, the data regarding responses of iron-deficient subjects stratified by the severity of anemia strongly support the contention that anemic and nonanemic iron-deficient subjects both benefit. In addition, compliance and side effects with intermittent supplementation appeared improved compared with daily supplementation. Whether intermittent supplementation can work prophylactically is still under consideration (14). Smaller, nontherapeutic doses of iron over longer periods of time (≥ 6 –8 mo) could be viewed as preventative of the "iron balance crises" that occur during pregnancy and to a lesser extent during the adolescent growth spurt and onset of menses. Such nontherapeutic

doses appear to reduce the risk of iron-loading pathologies. This approach might allow individuals to develop a more positive iron balance before such times in their lives when their iron requirements are particularly high and may be logistically viable when other interventions are precluded. 

REFERENCES

1. Basta SS, Soekirman M, Karyadi D, Scrimshaw NS. Iron deficiency anemia and the productivity of adult males in Indonesia. *Am J Clin Nutr* 1979;32:916–25.
2. Scholz B, Gross R, Sastroamidjojo S. Anaemia is associated with reduced productivity of women workers even in less physically strenuous tasks. *Br J Nutr* 1997;77:147–57.
3. Tobin B, Beard JL. Iron. In: Wolinsky I, Driskell J, eds. *CRC handbook of sports nutrition: vitamins and trace minerals*. Boca Raton, FL: CRC Press, 1996:137–56.
4. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomized study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet* 1996;346:992–6.
5. Beard J. One person's view of iron deficiency, development, and cognitive function. *Am J Clin Nutr* 1995;62:709–10.
6. Pollitt E, Saco-Pollitt C, Leibel RL, Viteri FE. Iron deficiency and behavioral development in infants and preschool children. *Am J Clin Nutr* 1986;43:555–65.
7. Walter T, Knovalsky J, Stekel A. Effects of mild iron deficiency on infant mental development scores. *J Pediatr* 1983;102:519–22.
8. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med* 1991;325:687–93.
9. Scholl TO, Hediger ML, Fischer RL, Shearer JW. Anemia vs iron deficiency: increased risk of preterm delivery in a prospective study. *Am J Clin Nutr* 1992;55:985–8.
10. Murphy JF, Newcombe RG, O'Riordan J, Coles EC, Pearson JF. Relation of hemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet* 1986;1:992–4.
11. Hernell O, Lonnerdal B. Iron requirements and prevalence of iron deficiency in term infants during the first 6 months of life. In: Hallberg L, Asp N, eds. *Iron nutrition in health and disease*. London: John Libbey Press, 1996.
12. Schultink W. Iron supplementation: compliance of target groups and frequency of tablet intake. *Food Nutr Bull* 1996;17:22–6.
13. Schultink W, Gross R. Iron deficiency alleviation in developing countries. *Nutr Res Rev* 1996;9:281–93.
14. Viteri FE. Effective iron supplementation does not happen in isolation. *Am J Clin Nutr* 1997;65:889–90 (letter).
15. Schultink JW, van der Ree M, Matulesi P, Gross R. Low compliance with an iron supplementation program: a study among pregnant women in Jakarta, Indonesia. *Am J Clin Nutr* 1993;57:135–9.
16. Brown EG Jr, Dubach R, Moore CV. Studies on iron transportation and metabolism. IX. Critical analysis of mucosal block by large doses of iron in human subjects. *J Lab Clin Med* 1958;52:335–55.
17. Wright AJA, Southon S. The effectiveness of various iron-supplementation regimens in improving the iron status in anaemic rats. *Br J Nutr* 1990;63:579–85.
18. Viteri FE, Xunian L, Tolomei K, Martin A. True absorption and retention of supplementation iron is more efficient when iron is administered every three days rather than daily to iron-normal and iron-deficient rats. *J Nutr* 1995;125:82–91.
19. Hallberg L. Combating iron deficiency: daily administration of iron is far superior to weekly administration. *Am J Clin Nutr* 1998;68:213–7.
20. Solomons NW. Daily versus weekly iron: we still might not be asking the right questions. *Nutr Rev* 1997;55:142–3 (letter).
21. Galloway R, McGuire J. Special report: daily versus weekly; how many iron pills do pregnant woman need? *Nutr Rev* 1996;54:318–23.

22. Viteri FE. Weekly compared with daily iron supplementation. *Am J Clin Nutr* 1996;63:610-4.
23. Solomons NW. Weekly versus daily oral iron administration: are we asking the right questions? *Nutr Rev* 1995;53:326-7 (letter).
24. Gross R, Schultink W, Juliawati H. Treatment of anaemia with weekly iron supplementation. *Lancet* 1994;344:821 (letter).
25. Berger J, Aguayo VM, Tellez W, Lujan C, Traissac P, San Miguel JL. Weekly iron supplementation in Bolivian school children living at high altitude. *Eur J Clin Nutr* 1997;51:381-6.
26. Palupi L, Schultink W, Achadi E, Gross R. Effective community intervention to improve hemoglobin status in preschoolers using once-weekly iron supplementation. *Am J Clin Nutr* 1997; 65:1057-61.
27. Schultink W, Gross R, Gliwitzki M, Karyadi D, Matulesi P. Effect of daily vs twice weekly iron supplementation in Indonesian preschool children with low iron status. *Am J Clin Nutr* 1995; 61:111-5.
28. Ridwan E, Schultink W, Dillon D, Gross R. Effects of weekly iron supplementation on pregnant Indonesian women are similar to those of daily supplementation. *Am J Clin Nutr* 1996;63:884-90.
29. Katelhut A, Schultink W, Angeles I, Gross R, Pietrzik K. The effects of weekly iron supplementation with folic acid, vitamin A, vitamin C on iron status of Indonesian adolescents. *Asia Pac Clin Nutr* 1996;5:181-3.
30. Liu XN, Kang J, Zhao L, Viteri FE. Intermittent iron supplementation in Chinese preschool children is efficient and safe. *Food Nutr Bull* 1995;16:139-46.
31. Gross R, Schultink W, Gross U. Reply to KL Gryboski. *Am J Clin Nutr* 1995;62:154-5 (letter).
32. ACC/SCN. Controlling iron deficiency. A report based on an ACC/SCN workshop. In: Gillespie S, Kevany J, Mason J, eds. Geneva: United Nations Administrative Committee on Coordination Subcommittee on Nutrition, 1991. (State of the art paper no. 9.)
33. Institute of Medicine and National Academy of Science. Report on prevention of iron deficiency anemia in pregnant women, women of reproductive age, and children. Washington, DC: National Academy Press, 1993.
34. Gutteridge JMC. Iron and free radicals. In: Hallberg L, Asp N, eds. Iron nutrition in health and disease. London: John Libbey Press, 1996:239-46.