

Letter to the Editor

Daily Versus Weekly Iron: We Still Might Not Be Asking the Right Questions

To the editor: I read with great interest the Special Report by Ms. Rae Galloway and Dr. Judith McGuire entitled "Daily Versus Weekly: How Many Iron Pills Do Pregnant Women Need?"¹ For those of us working in physiologic and biomedical investigation in developing countries, there is a compelling interest in the issue of how biologic insights are transformed into programmatic and policy decisions. It was the possibly premature introduction of programs based on the notion of alternate-day iron regimens into prenatal care around the world that prompted the authors to make a timely statement on the topic.¹

The authors did a heroic job of reviewing the literature and making a commentary in an area that, at the present time, does not yet have a critical mass of literature to evaluate. Of the "10 published studies on the efficacy of the weekly or intermittent iron dose," the authors point out that "two of the three Indonesian articles are in peer-reviewed journals" and that "the study by Liu et al. has been published in a peer-reviewed journal," noting that the other seven (70%) were in the form of meeting abstracts or letters to the editor. They give appropriately greater merit to the three papers published in full after peer review. I was then struck by an internal inconsistency later in their article. In the discussion of compliance with iron prescription (and without qualifying remarks), the "literature" cited as state of the art on that topic comes from four unpublished reports,²⁻⁵ all from the files of the nongovernmental agency that is the professional base of the lead author. I would caution the authors against the appearance of a "double standard" of rigor in appealing to the literature. What is sauce for the quantitative biomedical research goose should be sauce for the qualitative behavioral investigation gander!

Moreover, when the literature is scarce and of variable quality, the selective citation of material available in the area can produce further distortion. Hence, for a report published in *Nutrition Reviews*, it is of note that a Brief Critical Review I wrote the previous year for *Nutrition Reviews* was not consulted. My review⁶ provides further technical insights on the problems of the Cook and Reddy iron absorp-

tion study,⁷ performed in Kansas City women, in relation to the human implications of rodent work conducted by Wright and Southon⁸ and Viteri et al.,⁹ the latter two constituting the theoretical underpinnings of the public health approach to intermittent iron dosing. Beyond the lack of supervision of the daily iron supplement intake at home and the small sample size of the Cook and Reddy study,⁷ the interpretive significance of the Kansas City study is reduced by the lack of methodologic details, the single iron intervention cycle, the choice of the experimental meal, the low overall iron absorption responses in the subjects, and the dominance of the central tendency in the daily group by a single—possibly outlying—iron absorption value.

Although the quantity and quality of the literature cited is limited, Galloway and McGuire¹ provide an admirable synthesis of considerations and contexts with which to view the biologic findings. With the senior author of the report¹ based in the World Bank, however, I was surprised that there was not a more explicit economic analysis of the pros and cons of spaced iron dosing in their evaluative framework. I am certainly no economist, but to paraphrase what I wrote in my Brief Critical Review,⁶ if a lower dose is equivalent to (not different from) a higher dose of iron in its hematologic effects for maintenance or repletion, the lower dose is inherently better. Let us suppose that a future well-designed physiologic study in humans shows that spacing the iron dose and giving a respite to the intestine of only 24 hours produced a doubling of the efficiency of iron uptake from a 60 mg iron pill (a finding that would be consistent with published rodent work^{8,9}). If this were the case, taking a pill every other day would have the same cumulative effect as taking the same pill daily and would cost half as much in supplements.

Turning to the very important consideration of compliance, I point out a potential irony, namely, that nature's way might indeed be best. All parties decry the low and irregular compliance with iron pills prescribed for daily use as the motive for their concern with alternative dosing regimens. The au-

thors work with the assumption of a 50% compliance with daily iron among pregnant women in developing countries.¹ The above supposition of increased efficiency would then lead us to the possibility that women may already be enhancing the relative efficiency of uptake of the iron from their pills by skipping doses.

Is it premature for governments and private agencies to be converting their iron distribution to intermittent regimens? I think that even proponents of weekly dosing would agree with critics that the data to support such programmatic approaches are not yet in. As an interested bystander and occasional commentator on this multifaceted problem,⁶ I am glad that the interaction of intestinal physiology and human pill-taking behavior has been joined.^{1,6} This provides a framework for the eventual synthesis of valid and robust findings into policy. I agree with the authors¹ about the Herculean nature of any effort to change current patterns of iron self-administration by pregnant women in developing countries.

For me, on the one hand, the objective of the physiologic and pharmacologic work has more to do with accurately quantifying the dose-interval/iron-uptake characteristics of the human intestine than with imposing eventual weekly prophylactic regimens in at-risk communities. On the other hand, the pattern of how the irregular compliance occurs is, in fact, critical to any judgment about net iron uptake. We should all embrace further investigation into both the qualitative and the quantitative aspects of actual pill-taking compliance in low-income communities and publish findings in peer-reviewed journals. With two such sets of insights—one physiologic and the other behavioral—in hand, models (and then community trials) could be developed for how best to take advantage of any enhanced bioavailability of iron in spaced doses in the context of the kind of spontaneous spacing (pill omission) that already occurs in the real world of low-income pregnant women.

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