

# Iron needs during pregnancy: do we need to rethink our targets?<sup>1-3</sup>

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**ABSTRACT** This paper argues that current estimates of the need for absorbed iron, estimates of iron absorption, and hence estimates of iron requirements for pregnant women greatly depend on what is determined as the desirable or target hemoglobin concentration (goal). The existing goal appears to be based on the maximal hemoglobin concentration that can be achieved with iron supplementation of well-nourished women; this is a situation that can be expected to minimize iron absorption efficiency. I am unaware of attempts to define hemoglobin or anemia goals based on functional criteria (health of infant or mother). The current approach may seriously overestimate iron need and discourage food-based programs; furthermore, it may declare operational iron supplementation programs to be failures when, in fact, many programs may be successful in preventing functional effects of iron deficiency anemia. This is illustrated with data from a completed comparative study of daily and weekly iron supplementation. The final plea is to set aside existing traditions and, instead, attempt to develop functional criteria for anemia and establish functional goals of hemoglobin concentrations to be achieved during pregnancy. *Am J Clin Nutr* 2000;72(suppl):265S-71S.

**KEY WORDS** Iron, anemia, requirements, pregnancy, supplementation, hemoglobin

## INTRODUCTION

In this supplement, Bothwell (1) provides a good overview of current thinking about iron requirements during pregnancy. The factorial estimate of body iron needs during pregnancy has changed very little since the early 1970s when the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) committee addressed iron requirements for pregnant women (2). The factorial approach adopted in 1977 was again applied by a second FAO/WHO committee in 1988 (3). The only major change in the  $\approx 2$  decades between the first and second FAO/WHO reports was a considerably lower reported estimate of the amount of dietary iron that could be expected to be absorbed by the body. The estimated amount of absorbed iron was decreased from an assumed 20% absorption by iron-replete individuals consuming a high-availability diet and maintaining iron stores at concentrations stated in the 1970 report to  $\approx 7.5\%$  for individuals with comparable iron stores in the 1986 report; dietary iron needs were proportionately increased. This led the 1988 FAO/WHO committee to declare 2 further positions. First, that it is extremely unlikely that

iron needs in pregnancy can be met from dietary sources alone, even if the iron source has very high bioavailability. Second, that "unless stores of about 500 mg are believed to exist before pregnancy, administration of iron supplements may be indicated if impairment of the expected increase in hemoglobin mass is to be avoided," a view also expressed by Bothwell (1).

The 1988 FAO/WHO committee (3) made a new and important contribution to the discussion of iron requirements when it recognized and estimated needs for different criteria of requirements. Specifically, the committee offered estimates of dietary iron needs for the prevention of anemia and for the maintenance of unconstrained hematopoiesis as an indicator that all functional needs for iron were met. The committee explicitly declined to consider needs for the establishment and maintenance of iron stores. Although viewed as desirable, "the estimated levels of dietary iron needed to achieve such a state in all but the most highly bioavailable diets are very high. Thus . . . it was deemed to be more appropriate to estimate the dietary needs to prevent anemia as the second level of requirement." This, and the above assertion that direct iron supplementation during pregnancy is needed unless the preexisting iron store is  $\approx 500$  mg, indicates clearly that the 1988 FAO/WHO committee (3) was resigned to the apparent need for routine iron supplementation in pregnancy. Although I chaired both of the above committees, I admit to being very concerned that epidemiologic evidence, even just as a tool for validation of the factorial models, was not formally considered in the deliberations. The exception was Hallberg et al's (4) work showing that the amount of iron lost in menstruation, which is the major source of variation in absorbed iron requirements between women, could be related to the likelihood of anemia in Scandinavian women. This omission remains a serious issue that warrants discussion and perhaps dictates a need for reconsidering the published estimates of iron requirements of pregnant women, as well as for other groups, particularly as experience in developing countries increases. The objective of this paper is to try to raise awareness of this unmet need and to urge that serious attention be directed to it.

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Factorial approaches in estimating nutrient requirements are useful. Nevertheless, an attempt must be made to validate the assumptions and targets implicitly included in such approaches. Rush (5) correctly challenged some of the public health nutrition community's hard-held—but poorly documented—beliefs, and rightly pleaded for careful, open-minded reconsideration of the evidence on which the constructs have been built. Such an objective examination might lead to confirmation of existing positions, but it is also quite possible that a different position could emerge that would have profound bearings on supplementation programs in developing countries. Questions should be asked about current definitions of goals and approaches in estimating iron requirements during pregnancy.

Two key components of the factorial model warrant close examination in determining iron requirements during pregnancy: first, the estimates of dietary iron bioavailability, which are not unique to pregnancy and, second, the target hemoglobin concentration and, therefore, target hemoglobin mass in pregnancy. Most of the argument in this paper addresses the currently accepted targets for hemoglobin concentrations during pregnancy and their implications. It is at least possible, if not probable, that iron supplementation interventions are driven by the myth and assumption that bigger is better. Indeed, the evidence supporting current target hemoglobin concentrations in pregnancy is adequately summarized in the Food and Nutrition Board (6) report on nutrition during pregnancy. Discussing the hematologic findings of iron supplementation studies, the report describes unsupplemented women as “failing to meet their potential” and assumes that this is undesirable. The report states the underlying premise as, “iron administration, regardless of dose, will not raise hemoglobin concentration in the absence of deficiency.” It further specifies that “the acceptable goal for iron nutrition during pregnancy is simply to avoid progression beyond low iron stores to stages of impaired hemoglobin production.” This, of course, is the inferred situation when hemoglobin concentrations are below the individual's potential maximum concentration and, at a group level, hemoglobin is responsive to iron supplementation. Conventional cutoffs are defined based on an assumed person-to-person variation in these maximum concentrations. A potential for functional effects at this cutoff is mentioned in the Food and Nutrition Board report. However, the only documented functional effects in mothers or infants actually cited are at hemoglobin concentrations far below the accepted cutoff used to define anemia in pregnancy. This construct of estimating iron needs for real-world situations is challenged below.

If a need to achieve maximal potential hemoglobin concentrations can be supported with convincing evidence, then the arguments of this paper evaporate. Without such evidence, and unless the bigger-is-better dictum is accepted, iron needs in pregnancy may be seriously overestimated. This has unfortunate implications, particularly for the developing world.

#### HEMOGLOBIN CONCENTRATION TARGETS AND THE FACTORIAL ESTIMATE OF IRON REQUIREMENTS

The costs of absorbed iron in pregnancy, as estimated by the 1988 FAO/WHO committee, are shown in **Table 1** (3). Although some individuals may quibble about some of the numbers, the numbers have attracted broad consensus support. Table 1 pro-

**TABLE 1**  
Estimated costs of absorbed iron in a normal full-term pregnancy<sup>1</sup>

Fixed costs	
Basal losses from body	Generally taken as being equivalent to those of nonpregnant women. Average loss = 0.8 mg/d or 220 mg/pregnancy.
Fetal deposition	Full-term fetus contains ≈290 mg Fe. The rate of deposition varies with stage of pregnancy. Total iron deposited depends on birth size.
Placenta	Estimated to contain ≈25 mg Fe including entrapped blood.
Subtotal fixed costs	220 + 290 + 25 = 535 mg
Variable cost	
Expansion of red cell mass	Taken as iron needed to achieve an average hemoglobin concentration of ≈130 g/L at the end of pregnancy = 500 mg <sup>2</sup> .
Total cost	535 + 500 = 1035 mg

<sup>1</sup>From reference 3.

<sup>2</sup>Well-nourished women given iron supplements throughout pregnancy can achieve an average hemoglobin concentration approaching 130 g/L. This was the assumed target hemoglobin concentration for the factorial model of absorbed iron requirements.

vides a distinction between the fixed and the variable costs of absorbed iron during pregnancy. The former includes body excretory losses and iron deposited in the fetus and pregnancy-associated tissues, whereas the latter includes the cost associated with expansion of the red cell mass. Designating a variable cost to red cell mass expansion would not have been acceptable to the members of either of the FAO/WHO committees who addressed iron needs (2, 3). It should be emphasized, however, that few data exist to establish a link between filling the fixed cost compartment, and relative filling of the variable cost compartment as marked by maternal hemoglobin concentration. The exception is in severe anemia, which is usually considered as a hemoglobin concentration <70 g/L (6–8). In the presence of severe anemia, several findings are generally accepted as associated with the anemia and are seen as serious functional outcomes, although Rush (5) has challenged the causal linkage in some of these associations.

The costs of absorbed iron shown in Table 1 refer to estimates of absorbed iron utilization, including iron that may be drawn from stores, and are not estimated dietary needs. If only 5% or 10% of dietary iron is available for absorption, which reflects estimates often applied to typical diets in many developing countries that are low in iron absorption promoters and sometimes high in known inhibitors, then dietary iron intakes of ≈20–40 mg/d would be needed to meet fixed costs. An equal amount of iron would also be needed to provide for red cell mass expansion. The actual situation is even more serious because iron is not utilized at the same rate throughout pregnancy. Shown in **Table 2** are the calculated implied dietary iron needs, with iron utilization expressed per day by trimester of pregnancy, based on the dietary iron bioavailability data provided in the FAO/WHO report (3).

Depending on dietary iron bioavailability, the data in Table 2 shows that apparent dietary iron needs in the third trimester of pregnancy could be ≈60–125 mg/d in developing countries. Even

**TABLE 2**Estimated rates of iron utilization during pregnancy and implied dietary needs<sup>1</sup>

Trimester and component of use	Need for absorbed iron <i>mg Fe/d</i>	Implied dietary need by absorption degree		
		5% Absorption	10% Absorption	20% Absorption
First trimester				
Basal	0.8	16	8	4
Fetus and placenta	0	0	0	0
Red cell mass	0	0	0	0
Total	0.8	16	8	4
Second trimester				
Basal	0.8	16	8	4
Fetus and placenta	0.8	16	8	4
Red cell mass	2.7	54	27	14
Total	4.3	86	43	22
Third trimester				
Basal	0.8	16	8	4
Fetus and placenta	2.7	54	27	14
Red cell mass	2.7	54	27	14
Total	6.2	124	62	32

<sup>1</sup> Assuming a 55-kg woman. Data from reference 3.

in a Western setting, with high-iron-availability diets rich in animal products and low in iron inhibitors, the apparent iron need might be  $\approx 30$  mg/d. Such amounts are unlikely to be achieved through the diet by any woman. Committee after committee has admitted that it is estimating iron requirements that cannot be met through diet and, therefore, implicitly or explicitly, is recommending pharmaceutical supplementation. Bothwell (1) is more optimistic about iron amounts that might be absorbed from the diet during pregnancy, but he still concludes that dietary iron alone would be insufficient to meet the needs of absorbed iron. With dietary requirement estimates as high as those suggested in Table 2, even fortification cannot be expected to meet such intake targets. The possible exception would be when iron fortification increases stores in nonpregnant women to an extent sufficient to substantially subsidize the cost of a pregnancy (2).

The current numeric estimates of iron requirements during pregnancy drive public policy in a very direct way. Nevertheless, one must ask whether these estimates are justifiable. If it is correct to classify the hemoglobin mass expansion as a variable rather than a fixed cost of pregnancy, then the question must be asked, Does it really matter whether women achieve maximal potential hemoglobin concentrations?

There are 2 reasons the target hemoglobin concentration is so important. First, the target hemoglobin concentration and the total estimate of the physiologic need for absorbed iron are obviously linked. Second, if enough iron is introduced into the body to achieve current target hemoglobin concentrations, then the efficiency of iron absorption must also be reduced, which would increase the dietary iron intake needed to maintain this adequate status.

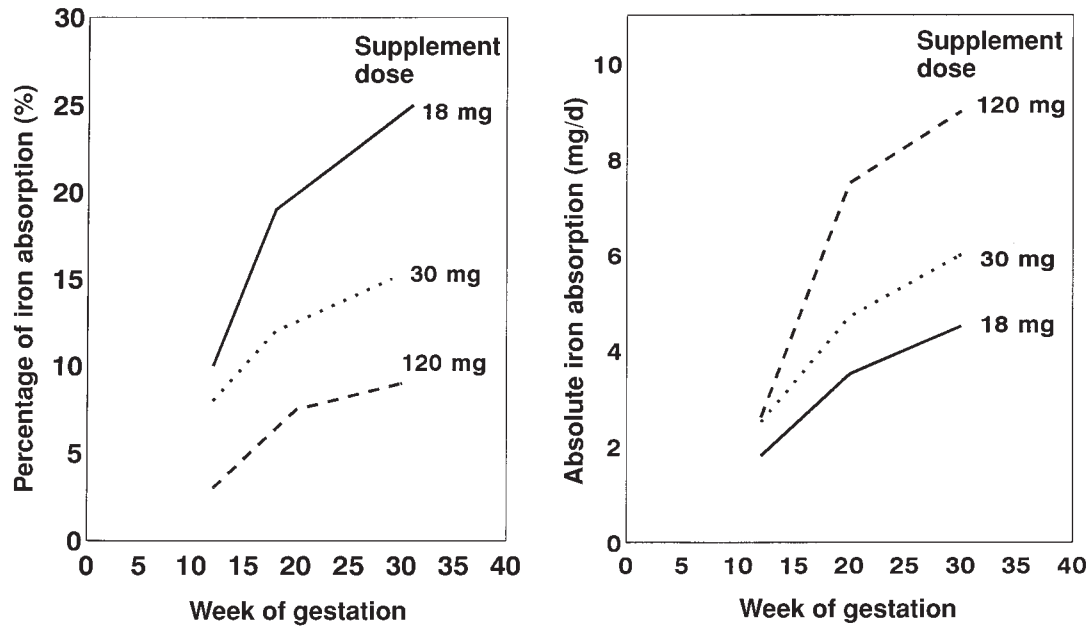
Consider iron absorption in pregnancy. In 1968 Heinrich et al (9) estimated the absorption of radioactively labeled iron in women at various stages of pregnancy. In these studies, the regulated capacity to absorb iron increased dramatically during pregnancy in parallel with the demand for iron. The estimated absorption of a test dose rose from 40% in the fourth month to 90% in the ninth month. The main contribution of this study was to show the existence of a functioning regulation of iron absorp-

tion in response to body iron need, just as such a system operates in nonpregnant subjects. In retrospect, Heinrich's subjects were almost certainly iron depleted by today's conceptual framework. This, too, would operate to increase iron absorption.

An earlier study by Hahn et al (10) estimated iron absorption during pregnancy as a function of both dose amount and stage of gestation. The results are illustrated in **Figure 1** as percentage of iron absorbed and absolute amount of iron absorbed. Iron absorption increases, with the stage of pregnancy as iron needs increase. Percentage iron absorption decreases as the supplement dose increases, but the absolute absorption also increases, which is a well-known and widely documented phenomenon in nonpregnant subjects.

The corollary of this portrayal is that at maximum potential hemoglobin concentrations, reflecting perhaps maximal absolute absorption, the expected efficiency of iron absorption is low. Thus, a high target iron utilization or high target hemoglobin concentration can be expected to increase dietary iron needs disproportionately. There is a maximal hemoglobin response in pregnant women, as is illustrated in **Figure 2**, which is based on data in the Food and Nutrition Board report (6). Note that among supplemented women, the group mean hemoglobin concentration increases slightly with dose, but the change is quite small. Note also that across these several studies, the unsupplemented control groups had mean hemoglobin concentrations in the range of 110–120 g/L compared with 125–130 g/L achieved in the supplemented groups. The question is, Is there evidence that a 5–15-g/L difference in group mean hemoglobin concentration is functionally important? This is one of the critical questions raised by Rush (5).

Simple calculations (**Appendix A**) suggest that for every 10-g/L change in hemoglobin concentration in the last trimester of pregnancy, there is a difference of  $\approx 175$  mg in the estimate of utilized iron (eg, estimates in Tables 1 and 2). This would represent a substantial difference in estimated dietary needs; a difference of 5–15 g/L in hemoglobin concentration might be equivalent to 85–260 mg Fe. Because it is likely that iron absorption decreases as the target hemoglobin concentration increases, there can truly be a dramatic effect on dietary iron requirements. To suggest that



**FIGURE 1.** Absorption of iron as a function of dose and stage of gestation. The left panel shows the efficiency of absorption and the right panel shows the absolute amounts of iron absorbed. Together, the panels illustrate the existence of an imperfect regulation of iron absorption governed by relative need for iron (stage of pregnancy) and load presented in the gut (dose). As dose increases in any stage of pregnancy, the efficiency of utilization falls sharply (left panel), but the total amount of iron absorbed increases (right panel). Data from references 6 and 9.

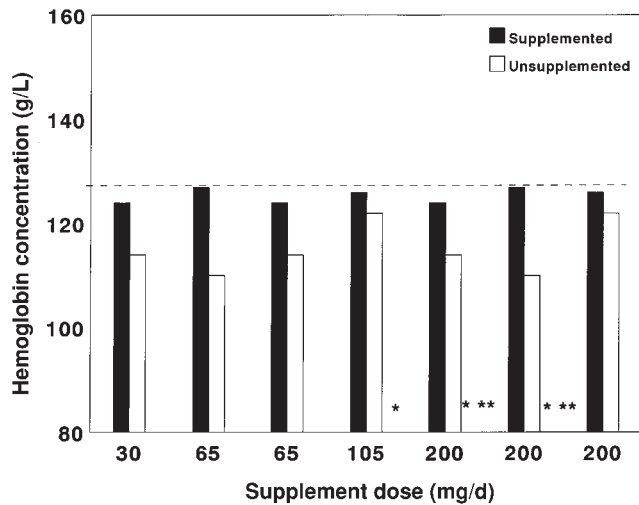
the increase in hemoglobin mass should be sufficient, at least to match the expected blood iron loss at delivery, is reasonable (8). Estimates for this have ranged from  $\approx 150$  mg Fe to  $\geq 500$  mg Fe (2, 3, 6, 8). If an arbitrary mean blood loss of 300 mg is assumed, and this is set as the target increment in circulating hemoglobin iron, the implied target group mean hemoglobin concentration would be  $\approx 110$  g/L. This is much lower than the existing target mean hemoglobin of 130 g/L and is lower than the mean hemoglobin reported for unsupplemented women in Figure 2. If a target mean concentration is set at 110 g/L, then the statistically defined cutoff ( $-2$  SD) might be between 90 and 95 g/L, which is well below the widely applied cutoff of 110 g/L. The only firm point to be made from this is that both a basis and a rationale exist for reconsidering target hemoglobin concentrations. Such reconsideration would seem to need an external marker of functional adequacy. Without such a marker, the arguments are largely circular—if the goal is set higher, more iron is needed; if more iron is given, higher hemoglobin can be achieved, but the human body may not need it.

#### OBSERVED HEMOGLOBIN CONCENTRATIONS IN DEVELOPING COUNTRIES

The current WHO (7) criterion for defining anemia during pregnancy is shown in Figure 3 along with the US Centers for Disease Control and Prevention (CDC) reference curve, which is based primarily on hemoglobin concentrations of supplemented north European women (11). CDC suggested that the WHO criterion be modified to allow for the dip in hemoglobin concentration midpregnancy. Perhaps more important than the position of reference concentrations at different stages of pregnancy is the recognition that both of the WHO and CDC references portrayed in Figure 3 are based on observations of iron-

supplemented women who are already deemed to be healthy and well nourished. Increasingly, anemia and now iron depletion without anemia are defined by values of iron status indexes and hemoglobin concentrations that can only be achieved with pharmaceutical supplementation, even in otherwise apparently healthy and well-nourished populations. This is the historical medical-biochemical approach to confirming a diagnosis of iron inadequacy and estimating iron intakes needed to prevent defined inadequacy. A second way to define anemia or iron depletion is to measure the hemoglobin concentration in populations accepted as healthy—ie, individuals without signs of iron depletion. The latter definition is the standard clinical chemistry approach to defining what is normal or abnormal, (atypical) concerning iron status. Both the medical-biomedical and clinical chemistry approaches have considerable support from tradition and neither approach, by itself, is appropriate; thus, both approaches must be examined critically. Before advocating what must be seen in physiologic and epidemiologic terms as extreme intervention measures of iron supplementation in the developing world, public health nutritionists need to ask, Does achieving the reference hemoglobin concentration during pregnancy really matter? Is it a valid goal that warrants the action being proposed? Such questioning should serve to focus greater attention on the contribution of iron to moderate and severe anemia, for which there appear to be well-documented functional associations. This is not to detract from the importance of reducing the burden of moderate and severe anemia, but only to question the importance of mild anemia.

An examination of the experience gained from weekly and daily iron supplementation is currently underway by Beaton and McCabe (GH Beaton and G McCabe, with the assistance and advice of S Zlotkin and R Yip, "Efficacy of Intermittent Iron Supplementation in the Control of Iron Deficiency Anemia



**FIGURE 2.** Relation between concentration of iron supplementation and circulating hemoglobin concentration in healthy pregnant women. Note the absence of any major dose-response effect over this dose range. Note also that the supplemented women reached an average hemoglobin concentration of 125–130 g/L, whereas the unsupplemented groups had average hemoglobin concentrations of 110–125 g/L. The data suggest that for most groups, iron supplementation raised hemoglobin concentrations by  $\approx 5$ –15 g/L. \* Sustained-release form; \*\*  $2 \times 100$  mg/d. Data from reference 6.

in Developing Countries: An Analysis of Experience. Final Report to the Micronutrient Initiative,” unpublished observations, April 1999). Preliminary analyses from 3 pregnancy studies, 2 in Indonesia and 1 in Africa, offer some salient results. With a pool of >1100 pregnant women randomly assigned to receive 1 of 2 modes of iron dosing, the data showed with reasonable assurance that daily supplementation was better than weekly supplementation. Nevertheless, it was also possible to suggest that the difference was so small (adjusted postsupplementation mean hemoglobin concentrations of 112 g/L compared with 110 g/L) as to be programmatically meaningless. This, however, is not the issue to be discussed at this time. More interesting, in the present connotation, are the final prevalence figures for anemia (hemoglobin <110 g/L): 51%, 57%, and 22% in the 3 pregnancy studies. If the criterion for defining anemia was reset at 90 g/L, which is the point at which current opinion suggests functional consequences of low hemoglobin concentrations may begin to become apparent, the prevalence figures become 0%, 9.3%, and 1.4% in the 3 studies, respectively.

Because it has been deemed unethical to withhold iron supplementation during pregnancy, none of these pregnancy trials included placebo control groups. As a result, judging true efficacy is not possible, and the 2 modes of iron administration can only be compared. In the Beaton and McCabe review (unpublished, 1999), an important question is, Were any of the iron supplementation programs effective or should weekly iron dosing be considered just as ineffective as everyone claims daily dosing to be? Bothwell (1) expresses serious doubt about the effectiveness of weekly supplementation, citing the failure of scale-up efficacious daily supplementation pilot studies to operational field

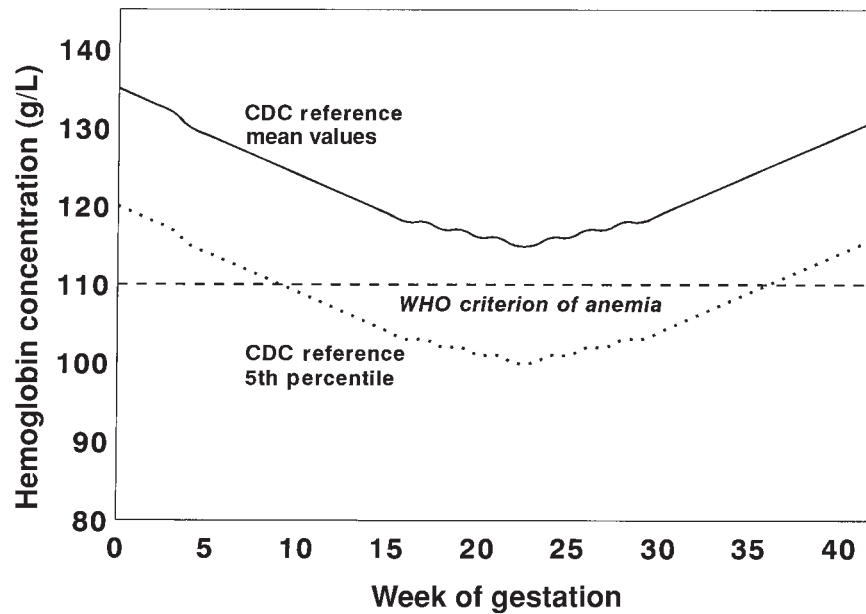
programs (12–14). Hallberg (15) expressed doubt that sufficient iron could be provided by weekly dosing. As is often pointed out, the most important concern in programs has been compliance in pill-taking behavior, and there is little to suggest that compliance will be better with weekly dosing than with daily dosing under operational program conditions. This complicates any inferences that might be drawn from the current efficacy trials analyzed by Beaton and McCabe. Rather than accept that iron supplementation, daily or weekly under operational conditions, is a general failure, a different argument is put forward here for consideration:

- 1) Both daily and weekly iron supplementation work in efficacy trial settings because the actual iron provided, generally 60 mg Fe/d or 120 mg Fe/wk, is substantially greater than needed. A smaller daily dose might also work just as well.
- 2) If the views expressed by critics are correct, ie, that weekly dosing cannot supply enough iron, then daily dosing would be expected to have a much higher differential benefit than has been seen. I would expect that a higher absolute level of iron administration in the presence of regulated absorption in anemic subjects would give the advantage to daily dosing. A major advantage was not seen consistently, however, when the group mean hemoglobin concentration, adjusted for initial hemoglobin concentrations, was the outcome measure. A highly consistent finding seen across 22 trials of children, adolescents, and adult pregnant and nonpregnant women, was that the post-intervention risk of being anemic (judged by WHO criteria) was higher in the weekly than daily supplemented group.
- 3) This line of argument may imply that reference hemoglobin targets have been set too high and that regulated iron absorption favors uptake from the weekly iron dose to meet physiologic needs. At the same time, high absorption from the daily iron dose is not facilitated to the same degree as the weekly iron dose and may actually be inhibited by the regulatory system. Both daily and weekly iron doses would be seen as providing more iron than actually needed. The final inference would be that more realistic hemoglobin targets need to be adopted. Perhaps these targets could be based on the concentrations seen in apparently well-nourished but unsupplemented women (8).

An alternate explanation that cannot be disregarded is that a substantial part of observed anemia is not iron responsive (16). This could account for the high numbers of women with residual anemia observed in these pregnancy studies.

Still another explanation has been recognized and given recent prominence. This argument states that it is impossible to normalize hemoglobin concentrations during pregnancy, regardless of iron dose or mode of administration, unless substantial pre-conception iron stores exist (1). This hypothesis suggests that preventive supplementation of all women of reproductive age be undertaken before pregnancy. It is not yet known whether this would be an effective approach, and it is certainly not known whether achieved benefits would justify the cost and effort of prepregnancy supplementation. Much would depend on the availability of evidence relating hemoglobin concentration during pregnancy to functional outcomes.

Separate from the assessment of daily compared with weekly iron supplementation, or even the proposal for preventive sup-



**FIGURE 3.** Reference hemoglobin concentrations in pregnancy. The horizontal line at 110 g/L represents the World Health Organization (WHO) cutoff that has been in place for  $\geq 25$  y and is now the most widely used criterion for anemia in pregnancy. The other pair of curved lines represent data from reference 11 based on studies of hemoglobin concentrations in iron-supplemented northern European women, complemented with data of early pregnancy gathered in the United States. The upper curve represents the estimated group mean hemoglobin concentration, whereas the lower curve represents the 5th percentile of the hemoglobin distributions, assuming an SD of 9 g/L (Ray Yip, personal communication, 1998).


plementation, are 3 issues that should be examined very carefully before intervention programs are planned:

- 1) Are operational programs now being declared as failures when instead they should be seen as successes?
- 2) Are iron requirements being overestimated and the potential for diet-based approaches being underestimated and, thus, is there a continuing insistence that relatively high-potency pharmaceutical preparations be mandatory?
- 3) Has the picture of iron deficiency anemia in pregnancy become so distorted that it is now viewed as an insurmountable problem?

## CONCLUSION

This paper ends as it began, with questions to be answered rather than with answers to be questioned. Emphasis was given to a point about which I feel very strongly. Public health nutritionists seem to have gotten caught up in the thinking that if a response, ie, an increase of hemoglobin concentrations in healthy populations, can be induced by giving what are, in physiologic and epidemiologic terms, incredible concentrations of pharmaceutical supplements, then it must be beneficial and that thus there is a moral and scientific obligation to advocate such a program.

I truly fear that we have managed to get ourselves and our research priorities very mixed up. The public health nutrition community must look hard at the evidence supporting the assumption that mild anemia in pregnancy has any functional significance. Without such evidence, I think it is scientifically unjustifiable—and perhaps immoral—to continue to claim that existing programs of iron supplementation are failing. The exception is in those cases that have shown that the oper-

ational infrastructure is not making supplements available on a continuing basis. If we continue to press the above assertions, we are likely to convince program planners and others that—even more than they now suspect—the problem of iron deficiency anemia in pregnancy is insurmountable. Unjustified claims for high (perhaps unreachable?) hemoglobin concentration targets are counterproductive and the public health nutrition community must find a way to break out of the box in which they have placed themselves. Rush (5) has given us the impetus that is collectively needed, and I thank him most sincerely for doing so. 

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## APPENDIX A

### Calculation of the difference in total iron content per 10-g/L change in hemoglobin concentration

According to Hytten and Leitch (1),

$$\text{Blood volume at 40 wk} = 5250 \text{ mL} \quad (1)$$

$$\text{Iron in hemoglobin} = 3.4 \text{ mg/g} \quad (2)$$

Difference in total iron content  
of circulating hemoglobin

per 10 g/L change in

$$\begin{aligned} \text{hemoglobin concentration} &= 5.25 \times 10 \times 3.4 \\ &= 178.5 \text{ mg} \quad (3) \end{aligned}$$

Hytten and Leitch (1) estimated that the total physiologic change in hemoglobin mass in unsupplemented but well-nourished women was equivalent to  $\approx 290$  mg; this may be compared with the FAO/WHO (2) estimate of 500 mg.

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