

# Iron Supplementation for the Control of Iron Deficiency in Populations at Risk

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*Iron supplementation, mostly with a therapeutic orientation, has been a key strategy for the short-term control of iron deficiency and ferropenic anemia. It has been used almost exclusively in antenatal clinics, but in spite of its confirmed efficacy in supervised trials, it has proven ineffective in practice in most developing countries. Poor effectiveness has been attributed to various factors including insufficient dose and time of supplementation and poor adherence. These problems have led to the administration of high iron doses, which have proven equally ineffective in practice. This paper introduces four concepts: (1) that iron supplementation targeted to pregnant women should cover the full reproductive cycle, from pre-pregnancy to at least the end of lactation instead of only the pregnant woman; (2) that entering pregnancy with iron deficiency contributes to the failure of antenatal iron supplementation and that prepregnancy iron reserves increase the effectiveness of antenatal supplementation; (3) that medium- to long-term weekly ingestion of proper iron-folate supplements, with a preventive aim and directed to all risk groups, should be community based rather than health service based but supervised by the latter (in this sense, preventive supplementation is equal to targeted iron fortification); and (4) that preventive supplementation, based on weekly dosing, has proven efficacious. Problem-oriented research to evaluate the sustainability and medium- to long-term efficacy of these concepts is called for. The bases for the concepts and suggestions are summarized in this paper.*

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## The Magnitude of Iron Deficiency and Anemia and Their Consequences

About 2.15 billion people suffer from iron deficiency and anemia, 85% of which is attributed to iron deficiency.<sup>1,2</sup>

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Thus, the overall prevalence of iron deficiency will be close to 34% of the 6.25 billion persons on our planet by the year 2000. Eighty percent of the total population reside in the developing world, where the prevalence of iron deficiency and anemia is almost fourfold that in the industrial world, which has an overall prevalence of 11%.<sup>2</sup>

It is well known that the age-sex-physiologic status groups at greatest risk are pregnant women, infants and toddlers, pubertal children, and women of childbearing age. The main reasons are dietary, because low intake and absorption of iron do not satisfy, in affected individuals, the iron requirements of growth, physiological blood losses, and blood volume adaptations and other events related to pregnancy and delivery.<sup>3,4</sup> In the developing world, greater infection rates, particularly hookworm, schistosomiasis, malaria, and other acute and chronic infectious diseases, aggravate the dietary limitations.<sup>5,6</sup>

The consequences of iron deficiency and anemia have been the object of several recent publications,<sup>7</sup> including those published herein, and the developmental implications of these conditions are also well recognized.<sup>2</sup>

## Measures to Control Iron Deficiency and Ferropenic Anemia

The general measures to control iron deficiency and ferropenic anemia practiced at present can be grouped into the following seven categories:

1. Improved dietary practices and lifestyles aimed at increasing iron intake and bioavailability and the adequate intakes of other nutrients involved in erythropoiesis, such as vitamin A, riboflavin, folate, and vitamin B-12. These practices should include breast-feeding; adequate amounts and varieties of foods in meals including heme iron-containing meat, poultry, fish, and other iron-dense foods in general and legumes and other vegetables in combination with foods rich in ascorbic acid; the avoidance of consumption of inhibitors of iron absorption in such meals (e.g., beverages rich in polyphenols and in calcium); cooking practices that reduce phytates and other polyphosphates that inhibit iron absorption, including heat treatment, fermentation processes, and seed sprouting; cooking in iron pots; food hygiene, which is particularly important where nutrient-dense and/or -fortified foods that fa-

vor bacterial growth are stored without adequate refrigeration; and, last but not least, increasing energy expenditure through physical activity and consequently increasing food intake without elevating the risk of obesity.<sup>8,9</sup> Layrisse and Garcia-Casal's contribution to this symposium, published herein, expands on this important category of control measures. It should be emphasized that feeding infants with unmodified or fresh fluid cow's milk, even if pasteurized but not heat-treated further, provokes gastrointestinal blood loss in a significant proportion of infants.<sup>10</sup>

2. Food fortification, including general or targeted approaches. This category of control measures is covered herein by Hurrell and in other recent publications.<sup>11, 12</sup>

3. Antenatal care and perinatal practices, including the prevention and control of gestational iron deficiency through iron supplementation at least during the second half of pregnancy; prevention of premature delivery, bleeding, and infection; delaying cord ligation; early contact to favor breast-feeding; and allowing adequate time between pregnancies.

4. Iron supplementation, which is the main topic of this paper. This has been practiced for more than 70 years and has been directed almost exclusively at the control of gestational anemia. Supplementation of infants and toddlers from weaning up to 3 years of age is now also advocated. In the case of low-birth-weight babies, iron supplementation is recommended from 2 to 3 months of age onward.<sup>13</sup>

5. Iron therapy, directed at treating ferropenic anemia and involving public and private health facilities. In many countries antenatal iron supplementation has a dominant therapeutic orientation.<sup>14,15</sup> Paramedical practitioners, including pharmacists, birth attendants, primary health workers, traditional healers, and household decision makers, play an important role in prescribing or purchasing iron preparations with a therapeutic aim upon suspicion of iron deficiency and anemia. The levels of training, understanding, and awareness of the problem of iron deficiency and anemia vary greatly among these persons as well as among all health providers<sup>16</sup> and affect therapeutically oriented iron supplementation programs. In spite of the variety of participants in this category of control measures, the World Health Organization estimates that in the developing world 47% of the rural population does not have access to health care facilities.<sup>17</sup> Moreover, the efficiency and coverage of daily iron supplementation by health facilities are low. There is clearly a need for innovation in the practice of antenatal iron supplementation involving community groups outside the health establishment.

6. Environmental sanitation and control of infections. These should play important roles in efforts to control iron deficiency, including control of parasitic diseases (see Stoltzfus herein); repeated bacterial and viral infections,

so common in children of the developing world; and chronic bacterial and viral diseases including tuberculosis and AIDS.

7. Health and nutrition communication and education directed to decision makers, leading economic and social forces (advocacy at the political level), health providers, and the public at large. There is an urgent need for this kind of action, which has been neglected in most countries of the developing world.<sup>18,19</sup>

## Evaluation of Past and Current Iron Supplementation Situations

The practice of iron supplementation arose with the therapeutic management of gestational anemia and has remained the main, and often the only, intervention aimed at controlling iron deficiency and anemia in most of the developing world. Gestational anemia is considered apart from the iron nutritional health of women of childbearing age. There is no doubt that data derived from clinical and field trials demonstrate that daily iron supplementation provided in a variety of doses is efficacious in pregnancy. However, iron supplementation appears to be ineffective in reducing iron deficiency before, during, and after gestation. Prevalence figures published in 1992 by WHO show that a high proportion of pregnant women and women of childbearing age suffer from anemia.<sup>20</sup>

Several factors are cited as responsible for this situation, including inadequate coverage of populations in need of services, lack of political commitment and financial support, deficiencies in supply and distribution of supplements at health centers, cultural and health beliefs of providers and recipients, inadequate training of providers, education of recipients, color and other characteristics of the supplements, and, last but not least, undesirable side effects associated with the daily intake of iron.<sup>16</sup>

With regard to country programs to control iron deficiency, a survey of health professionals who were in positions that could influence health policies and who were also considered the best informed in 35 Latin American and Caribbean countries and six other countries (China, India, Indonesia, Nigeria, Tanzania, and Thailand)<sup>21</sup> found the following: 71% of the countries had nationally or regionally structured antenatal iron supplementation programs; the effort placed on these programs was perceived to be inadequate; the median overall operational effectiveness (percentage coverage multiplied by the percentage compliance) was estimated to be 19%, except in the English-speaking Caribbean, where it was 48 %; many programs had an exclusive therapeutic approach; and improvement was to take place mostly through "health centralized and health center-based operational reforms and support" in spite of convincing evidence that the more successful programs in terms of sustainability, operational coverage, and impact in controlling gestational anemia and

malarial infections are community based.<sup>22-24</sup>

These findings confirm the predominance of therapeutic rather than preventive approaches, the medical orientation of antenatal supplementation, and the lack of concern with iron deficiency in women outside of pregnancy, despite ample evidence that iron deficiency produces serious functional limitations in them<sup>25,26</sup> and that good prepregnancy iron status is essential in controlling gestational anemia.<sup>27</sup> Moreover, the majority of health authorities who can influence and implement antenatal and other iron supplementation programs tend to ignore the importance of community involvement and the preventive orientation that iron supplementation programs should have.

In 1989, WHO recommended the universal iron supplementation of pregnant women (60 mg elemental iron and 250 mg folic acid once or twice daily) through the primary health care system.<sup>28</sup> The twice-daily regimen was recommended where gestational anemia was common (i.e., most of the developing world). Currently (1996), 60 mg iron/day is recommended if supplementation is started before mid-pregnancy.<sup>13</sup> A 1989 WHO document states that “in large-scale public health programmes, particularly in developing countries, where systematic laboratory testing is organizationally and financially impossible ... the approach that is more cost-effective is to give iron supplements to entire high-risk groups, particularly pregnant women. With this approach the distinction between treatment and prevention is blurred as supplementation will act to reverse anaemia in some individuals and prevent it from developing in others.”<sup>28</sup> In other words, the doses proposed for the prevention and the treatment of anemia are the same.

In many industrialized countries, antenatal iron supplementation is not compulsory, the recommended daily doses are smaller (often on the order of 30 mg elemental iron), and supplementation is prescribed only if anemia is detected.<sup>29</sup>

The 1989 and 1996 WHO documents referred to above<sup>13,28</sup> also state that for adolescents and adults (women for preventive purposes and both sexes for therapy), the recommended dose is 60 mg elemental iron/day in cases of mild anemia or when anemia prevalence is less than 20% and double that dose when anemia is moderate/severe or the prevalence is greater than 20%. In these groups both documents recommend a 2–4-month course of supplementation repeated every year or when needed because of anemia. In the case of preschool-age and school-age children, both documents recommend supplementation with 2 mg elemental iron/kg/day or 30–60 mg elemental iron/day “for a 2 to 3 week course several times a year,” depending on the age of the child, as a preventive or therapeutic approach.

In the case of normal breast-fed infants, iron supplements are recommended starting between 4 and 6 months and ideally continuing up to 24 months of age. This applies where weaning foods, fortified or not, provide less iron

than recommended and where milk- or soy-based formulae are not iron fortified. International health agencies recommend that where the prevalence of anemia is higher than 20% among infants, iron supplementation should be universal at a dose of 2 mg/kg/day. Essentially all of the developing world and many industrialized countries meet this criterion. Where anemia prevalence is lower, they recommend a dose of 1 mg/kg/day. In the industrialized world, the American Academy of Pediatrics recommends that supplementary iron in all infants should start at 4–6 months of age at a 1 mg/kg/day dose and double the dose for preterm infants, not to exceed 15 mg/day up to 1 year of age.<sup>30</sup> In the latter infants, supplementation should also start earlier, usually by 2 months of age, but in very-low-birth-weight infants it can be started as early as 3 weeks of age provided that vitamin E intake is adequate.<sup>31</sup>

In spite of the above recommendations, iron supplementation to groups other than pregnant women is uncommon worldwide. To our knowledge, there are no systematic iron supplementation programs anywhere directed to school-age children, adolescents, and women of child-bearing age.

## Evaluation of Recommended Iron Supplementation Doses During Pregnancy

### Estimates of Iron Needs in the Reproductive Cycle and Their Fulfillment

Iron needs increase substantially beginning in the second trimester of pregnancy and reach their peak during the third trimester. Estimates of total iron needs to prevent iron deficiency during pregnancy and immediately after delivery, including intrapartum and puerperal blood and iron losses, vary significantly,<sup>32,33</sup> from 660 to 1640 mg. Median total iron needs are estimated to be around 1000 mg, i.e., 640 mg above median prepregnancy needs. However, the evaluation of iron status and anemia in pregnant women is carried out during gestation, with the last evaluation taking place near term. In evaluations of the amount of iron needed to prevent iron deficiency during pregnancy, delivery and puerperal blood iron losses should not be considered. Therefore, median total iron needs during pregnancy are 840 mg (Table 1) because they are reduced by an average delivery and puerperal losses of 250 mg (range 90–310 mg). Median intrapregnancy needs above prepregnancy needs amount to a median of 476 mg. Iron requirements during the last 6 months of pregnancy amount to 4.6 mg/day if no iron from reserves is to be used. This is 3.3 mg/day above median prepregnancy daily needs.

Because median iron needs should be considered throughout a reproductive cycle (from conception through lactation; see Table 2), maintenance for 4 months of postpartum amenorrhea plus 2 months with menses should be considered as well as intrapartum and puerperal blood and

**Table 1.** Estimated Women's Needs for Iron (mg) During Pregnancy Above Those of Menstruating Women

	Median	90th percentile <sup>a</sup>
Maintenance during amenorrhea	190	210
Fetal iron	270 <sup>b</sup>	400
Placental iron	80	150
Hemoglobin and tissue expansion	300	450
Total	840	1210
Total mg above prepregnancy	476	566
Daily iron needs during last 6 months of gestation (mg/day) <sup>c</sup>	4.6	6.7
Daily iron needs above prepregnancy during last 6 months of gestation (mg/day)	3.3	4.4

<sup>a</sup>For 90th percentile in every variable.

<sup>b</sup>For a median birth weight of 3.33 kg and 81 mg iron/kg.

<sup>c</sup>If needs are satisfied in their totality without recurring to iron reserves, daily iron needs during the last 6 months of pregnancy.

iron losses (median 250 mg) and breast milk iron (54 mg in 6 months of lactation). Likewise, the iron gained from involution of the maternal erythrocyte mass and other tissues (median 300 mg) should also enter the equation.

Considering all of these factors, the median postpartum iron balance is +57 mg, mainly from postpartum involution.

Therefore, the median total iron requirements for a full 15-month reproductive cycle (9 months of pregnancy and 6 months of lactation) are 1018 mg. This constitutes 426 mg above the median iron needs for 15 months prior to pregnancy, or 0.94 mg/day. If only gestational needs are considered and these must be satisfied only during the last 6 months of pregnancy, 3.3 mg/day above the median prepregnancy iron needs is required. Thus, considering a whole reproductive cycle as a unit for iron balance reduces the iron needs above the prepregnancy state to one-third those estimated to cover only pregnancy needs if these are to be satisfied exclusively during the last 6 months of gestation. These rise to 5.2 mg above prepregnancy iron needs if only the last 3 gestational months are believed to

be available to cover iron pregnancy costs.

Other factors must be considered in determining the recommended doses of iron supplementation during pregnancy. One is that during pregnancy levels of erythropoietin naturally increase and are higher with anemia,<sup>34</sup> and another is that food iron absorption is enhanced by erythropoietin, iron deficiency, and anemia.<sup>35,36</sup>

#### Physiologic Factors That Favor Iron Balance During Pregnancy

Considering the above estimates of iron needs and the physiologic adaptations during pregnancy and lactation, it would appear that the amount of absorbed iron required during pregnancy and especially during a full reproductive cycle could be met in the presence of adequate prepregnancy iron reserves and consumption of a favorable diet. This is what Barrett et al.<sup>37</sup> suggest from their studies with stable iron isotopes on iron absorption in nonanemic British pregnant women. Mean geometric absorptions from a breakfast of meat, bread, and orange juice providing 3.2 mg iron and enriched with 2.8 mg <sup>54</sup>Fe for a

**Table 2.** Women's Needs for Iron (mg) During a Full Reproductive Cycle and Their Total Above Those of Menstruating Women

	Median	90th percentile
Pregnancy (total)	840	1210
Postpregnancy (total) <sup>a</sup>	478	606
Total	1318	1813
Fe recovery from contraction of Hb mass	(300) <sup>b</sup>	(450) <sup>c</sup>
Grand total	1018	1366
Fe losses in 65 weeks during menstruation <sup>d</sup>	(592)	(1046) <sup>e</sup>
Totals above those of menstruating women	~426	~320 <sup>e</sup>
Pregnancy only during last 6 months of gestation (mean/day)	~3.3	~4.4
Reproductive cycle in 452 days (mean/day)	~0.9	~0.7

<sup>a</sup>Birth, puerperium, and 25 weeks of lactation, 17 of which are without menses.

<sup>b</sup>Median mg Fe for Hb expansion during pregnancy in nonanemic women.

<sup>c</sup>mg Fe for Hb expansion during pregnancy in 90th percentile women.

<sup>d</sup>Median daily Fe needs = 1.3 mg; 90th percentile = 2.3 mg. Values are for 40 weeks (equivalent to pregnancy) and for 65 weeks, equivalent to a full reproductive cycle that includes 25 weeks of lactation.

<sup>e</sup>If woman has menstrual losses in the 90th percentile.

total of 6 mg iron were 7%, 36%, and 66% at 12, 24, and 36 weeks gestation.

By contrast, Svanberg et al.<sup>38</sup> reported that in non-iron-deficient Swedish pregnant women, nonheme food iron absorption levels were 5.8% in the second trimester and 14.4% in the third trimester. The diet provided 17 mg iron, of which 1.2 mg was heme iron. Note that one-quarter of all women studied absorbed more than 20% of the nonheme iron and that the upper quartile of iron absorption was as high as 5 mg/day. On average, most women in this study would have absorbed around 300 mg dietary iron in the last two trimesters of pregnancy (or an average of only 1.7 mg iron/day) plus about 22 mg iron in the first trimester, thus entering into a negative iron balance of 511 mg if they had no iron reserves to start with. This would be translated into ferropenic anemia at term (a deficit of 43 g hemoglobin [Hb]/liter). Among the “high absorbers,” about 595 mg dietary iron would be absorbed in the last two trimesters of pregnancy (an average of 3.3 mg iron/day) plus about 50 mg iron in the first trimester. These women would still be about 195 mg short of satisfying the 840 mg iron that pregnancy per se requires, and would develop a “mild anemia” because a deficit of 195 mg iron would be translated into a Hb deficit of 16.0 g/L in an average 55 kg pregnant woman. Mean Hb at term would be around 108 g/L.

In the United States and Europe,<sup>39,40</sup> between 16% and 32% of fertile-age women have no iron reserves at all and only 40–60 % of childbearing-age women have iron reserves of 300 mg or more. In rural and urban Guatemalan childbearing-age women, these proportions range between 32% and 75% and between 12% to 18%, respectively.<sup>41</sup> If “average” women entered pregnancy with 300 mg iron reserves and they absorbed only the mean of what Svanberg et al. estimate,<sup>38</sup> they would have a –211 mg iron balance at term. This would be reflected by a Hb level 17.3 g/L below that of an average 55 kg woman maintaining iron balance. Supplemented pregnant women in the industrial world have an average Hb level of  $124.6 \pm 4.3$  g/L,<sup>29</sup> and this hypothetical woman’s Hb level would be 107.3 g/L, which, again, is a mild gestational anemia. With 300 mg prepregnancy iron reserves, the “high absorbers” would still have slightly more than 100 mg iron reserves at term, but the median woman would still finish pregnancy with a moderate negative iron balance.

This situation would not hold if iron needs during the whole reproductive cycle are taken into account. Much of the deficit incurred during pregnancy is recoverable during the postpartum period and the ensuing 6 months. There is evidence in the literature to support this assertion.<sup>42</sup>

In the absence of iron reserves and even in the presence of mild-moderate deficiency but no prepregnancy anemia in the developing world, and disregarding the fact that women are generally smaller and thus have somewhat lower basal needs, absorbed iron from supplements should be around 500 mg on top of the absorbed dietary iron. The

recommended dose of 120 mg elemental iron/day for the last two trimesters would provide 21,600 mg iron. To satisfy the extra 500 mg iron needed, only 2.3% of supplemental iron needs to be absorbed. This means that the gut would be constantly filled with 117 mg unabsorbed iron every day, which is undesirable. Even if during pregnancy Hb were repleted from 80 to 110 g/L (therapy on top of maintenance in this case), 1000 mg iron needs to be absorbed. This is only 4.6% of the total recommended iron dose. If only 3 months or less of iron supplementation could be implemented because of late admission to antenatal care, only 5–10% of the 120 mg daily dose (6–12 mg) needs to be absorbed and 90–95% would be constantly present in the gut. Theoretical estimates for allowing daily increments of 1 g Hb/L blood after the fourth day of therapy<sup>28</sup> would require about 15% absorption of the daily 120 mg dose in the third trimester, to bring total daily iron absorption to 12 mg. Norrby<sup>43</sup> in his classical studies on iron therapy in acutely iron-depleted subjects found that in moderate anemia a response of no more than 2 g Hb/L per day could be observed. Thus, for a moderately anemic (Hb 80–100g/L) 55 kg woman, only 24 mg iron could be utilized for hemoglobin synthesis daily. Thus, in the third trimester no more than 30 mg iron/day need be absorbed to observe a rapid therapeutic effect (a rise of about 20 g Hb/L in 2 weeks). This amounts to 25% absorption of the 120 mg daily dose. Still, 90 mg iron would be constantly maintained in the gut, which is six times the usual iron intake of 15 mg/day.

### Evaluation of Current Practices of Daily Iron Supplementation in Pregnancy: Clinical and Field Trials

Clinical and supervised field trials<sup>29</sup> have provided solid evidence that iron supplementation during pregnancy is efficacious in protecting and improving iron nutritional status during and after pregnancy. These studies have tried to define the best iron dose, alone or in combination with other hematinic nutrients,<sup>44</sup> in reducing the rate of anemia at term in different populations. In some cases serum ferritin has also been determined. It must be clear that these trials, with few exceptions, have not been designed to test the effectiveness of iron supplementation programs but, instead, to test the efficacy (or biological effectiveness) of iron supplementation.

There are ongoing debates regarding the aims of iron supplementation, the more efficacious doses and nutrient combinations, and whether high daily iron intakes are desirable in the light of possible side effects and possible interference with absorption and metabolism of other minerals, nutrients, and food substances. The debate on these issues translates into policy positions regarding whether iron supplementation during pregnancy should be universal or selective; if the latter, on what basis and with what doses.

These questions have no easy answers. They depend on whether the objectives of interventions are (1) to prevent and correct anemia so that at term hemoglobin levels are higher than those associated with health risks for mother, fetus, and infant (Hb levels above 90 or 100 g/L provide a margin of safety), (2) to prevent and/or correct anemia at term, defined by an accepted Hb cutoff point (110 g/L at sea level, but poorly defined at higher altitudes), (3) to prevent depleted maternal iron stores at term, or (4) to achieve “maximal expansion of erythrocyte mass.”

Studies to determine the most desirable supplementation doses of iron alone and in combination with other nutrients have resulted in very different recommendations depending on the characteristics of the populations studied. The recommended doses have ranged between 30 and 240 mg/day depending on the aims of the supplementation, its duration, and the severity and prevalence of iron deficiency and anemia that the pregnant population presents with at the start of the studies. The general tendency has been to recommend large doses of iron in populations where prepregnancy anemia rates are high and where the period of supplementation is short. These high doses have been limited by the incidence of side effects and by the possible effects that such high doses may have on the absorption and metabolism of other nutrients and food substances.<sup>45,46</sup>

Side effects increase in an almost geometric fashion with the daily dose,<sup>45</sup> so that tolerance limits the daily amount of supplemental iron that can be administered and leads to poor adherence and rejection of supplements. There have been several attempts to reduce side effects through producing special pharmaceutical preparations. The latest iron preparation that has proven somewhat successful in reducing side effects has been the gastric delivery system (GDS) by which ferrous sulfate is made to float in the stomach contents. Under these conditions, iron appears to be absorbed better because of its slower release to the gut.<sup>47</sup>

Last, the efficacy of iron supplements varies depending on (1) the quality of the dietary iron, (2) the presence of other conditions that may limit iron utilization, such as other nutritional deficiencies, (3) the time, in relation to meals, when the supplements are ingested, (4) what combination of nutrients is included in iron-containing supplements (energy, protein, amino acids, vitamins, and minerals) that may favor or impair iron absorption and utilization, and (5) the period of pregnancy when supplementation takes place.

Several general conclusions can be derived from these studies:

1. There is no universally recommended specific iron supplementation dose.
2. The objective should be to find the smallest iron supplementation dose that accomplishes the stated

aims of the supplement, considering the greatest safety and tolerance margin.

3. Determinants of the success of a given dose are the number of weeks the supplement is ingested during pregnancy as well as, within limits, the total amount of supplemental iron ingested.
4. Consideration must be given to the possibility that the presence of other conditions may limit the response and that a combination of nutrients may be required for optimal results.
5. Most importantly, the iron status of the women at the start of a supplementation program greatly influences its outcome.

## The Concept of Preventive Supplementation

This concept evolved from three main streams of thought:

1. The ineffectiveness of antenatal iron supplementation programs and its possible relation to the apparently unnecessarily high iron levels recommended by WHO could be causing pregnant women to (a) reject supplementation because of side effects, (b) transmit a negative message to their peers with the consequent low demand for iron supplements in prenatal services, and (c) generate a negative attitude and poor motivation of suppliers of care for this specific strategy.

2. There may be the perception or the realization that there is no significant progress in the developing world in controlling iron deficiency and anemia; that in these areas of the world, coverage of at-risk populations by health services is low and that their effectiveness in antenatal supplementation programs is even lower; that many years will pass before the diet in the developing world becomes adequate in terms of iron bioavailability and that food fortified with iron will not be available for many years to large populations at risk of iron deficiency; and that even then, a significant proportion of childbearing-age women and children will exhibit inadequate iron reserves, iron deficiency, and anemia.

3. Conceptually, given the already high demands for iron during pregnancy, it is inefficient to try to correct prepregnancy iron deficiency during gestation, particularly by giving large doses of iron that carry a high proportion of side effects and, possibly, rejection of the supplements. The concept should be one of “preventive supplementation” aimed at ensuring adequate iron nutrition throughout a woman’s life cycle, especially in relation to her reproductive cycle or cycles, which make her especially vulnerable to iron deficiency and ferropenic anemia during her childbearing years. This concept can (and should) be extended to the other at-risk populations, including infants, toddlers, and adolescents.

Given the negative individual and societal consequences of iron deficiency and ferropenic anemia, it would

be a mistake simply to accept the present situation or to have to wait for decades to control it.

The first line of thought led to the investigation of the dynamics of iron absorption and utilization of iron supplements in an iron-normal and iron-deficient rat model.<sup>48</sup> The supplementation doses were adjusted to mimic the recommended doses for universal supplementation in populations where iron deficiency is common, which is 120 mg iron daily for pregnant women. The hypothesis was that with these large doses the intestine would become loaded with iron, blocking the absorption of repeated iron intake, as has been shown in other experimental animals and humans.<sup>49-51</sup>

The second line of thought led to the development of “preventive supplementation”<sup>52-54</sup> as an operative possibility where food-based strategies for controlling iron deficiency are not available now and do not appear to be a reality in the foreseeable future. The ideal case would be if all women of childbearing age entered pregnancy with adequate iron reserves. If this were the case, iron supplementation would easily prevent the development of iron deficiency and anemia during pregnancy, and infants would be born with better iron reserves, also making the prevention of iron deficiency easier at that critical age.

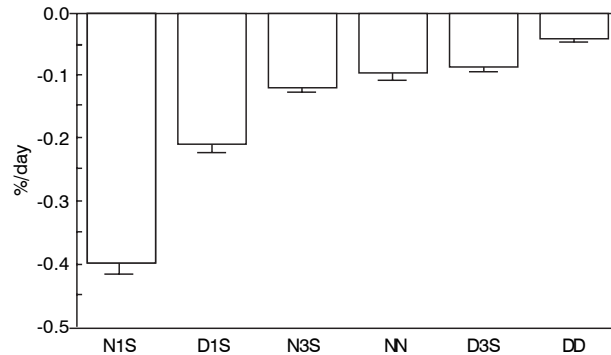
How can this be accomplished? By convincing child-bearing-age women (and teenagers where teenage pregnancy is a problem) to take a 60 mg iron tablet once a week for several months (or years) before they become pregnant. Theoretical calculations would suggest that with this dose and with the ability to regulate absorption depending on iron nutritional status, these women could ultimately have the same prevalence of iron deficiency as men (< 2%) and could develop some iron reserves. A reasonable estimate would be the absorption of 10% of the 60 mg dose, which would provide 6 mg extra iron/week, or the equivalent of nearly 0.9 mg iron daily. This amount added to the absorbed dietary iron would cover the menstrual iron losses of more than 90% of women.

Both lines of thought converged in trying to find the simplest, most efficacious, tolerable, and safe iron supplementation schedule for the prevention of iron deficiency in populations at risk, *with active community involvement*. This approach could complement the primary health approach of iron therapy and therapeutically oriented supplementation.

### Summary of Some Investigations of the Dynamics of Supplemental Iron Absorption and Utilization in Experimental Animals

#### Iron Absorption and Rates of Body Iron Loss<sup>48</sup>

In a study involving iron-normal and iron-deficient rats receiving an FeSO<sub>4</sub> supplement as a premeal before receiving an iron-free meal twice daily, iron absorption and utili-



**Figure 1.** Daily iron rate of loss of retained whole-body iron in iron-normal and iron-deficient rats supplemented with iron daily or every 3 days in doses equivalent to 120 mg iron in a pregnant woman. From reference 48. N1S = iron-normal supplemented daily; D1S = iron-deficient supplemented daily; N3S = iron-normal supplemented every 3 days; NN = iron-normal; D3S = iron-deficient supplemented every 3 days; DD = iron-deficient.

zation were studied by means of whole-body counting of trace doses of <sup>59</sup>Fe added to the premeal. Weanling Sprague Dawley rats were trained to meal-feed twice daily. The premeal contained either no iron (iron-deficient) or 400 µg iron (iron-normal) or 4000 µg iron (iron supplemented). In total, the supplemented rats received an amount similar to the 120 mg iron recommended to pregnant women who usually consume 12 mg dietary iron.

Results showed that in iron-normal rats supplemental iron absorption was essentially stable during the first 4 days of supplementation and reached a lower stable absorption level from the seventh day onward. In contrast, in the iron-deficient rats supplemental iron absorption decreased exponentially after the first dose, reaching absorption levels similar to those of the iron-normal supplemented rats also from the seventh day onward. Overall, 13-day absorption efficiencies were 6.05% and 8.17% (total absorbed iron/total ingested iron) for iron-normal and iron-deficient animals. The speed at which iron absorption declined was surprising, reinforcing and expanding in detail the iron blockage described in other studies.<sup>49,50</sup> It also reinforced our initial belief that it made little sense to provide large doses of iron when less than 10% was absorbed in both groups of rats after the first 7 days of supplementation, leaving more than 90% of this iron in the gut. Importantly, in the iron-normal and iron-deficient supplemented rats, rates of body iron loss after unabsorbed mucosal iron was excreted were 4.1 and 2.2 times the rates observed in normal rats (Figure 1).

These results suggested that in order to increase the efficiency of iron absorption and utilization, either lower daily supplementary iron doses should be administered or the usual supplementation doses should be administered intermittently, trying to avert iron blockage by administering the doses in synchrony with the turnover of the small-intestinal mucosa, which in the rat is close to 3 days. The

hypothesis was that by presenting supplemental iron only to new cells not previously loaded with iron, absorption would be optimized. We decided to follow this route of research and proceeded to repeat the studies on iron absorption and body iron loss in daily-supplemented rats but this time in rats receiving 10 times the normal iron intake only once every 3 days. The cumulative absorption efficiency in 13 days of supplementation among the iron-normal rats increased by 60%, and in the iron-deficient rats it more than doubled. In these rats, the progressive fall in iron absorption as the number of supplementation days increased was almost linear, in contrast to the logarithmic loss observed with daily supplementation.

The overall mean absorption by iron-normal supplemented rats was 9.6% in the every-3-day regimen compared with 8% in the daily regimen (the latter average absorption was 82.5% that of the former). In the iron-deficient rats the overall mean absorptions were 15.1% and 9.9%, respectively (the latter being 65.5 % that of the former).

Body iron losses were also markedly reduced by the every-3-day regimen, further increasing the overall efficiency of the intermittent schedule (Figure 1).

#### Iron Contents in the Gut and in the Liver<sup>55</sup>

Overnight fasted rats were anesthetized and sacrificed at different intervals of iron supplementation, by blood extraction from the aorta, after an overnight fast. Their liver and small intestines were removed, and the gut contents were washed with cold saline and 0.3 mol Na<sub>2</sub>EDTA solution followed again by cold saline solution to wash out the iron in the intestinal lumen. The gut was divided into the duodenum, upper and lower jejunum, and upper and lower ileum. Nonheme iron in liver and intestinal mucosal scrapings from each segment were measured. Significantly higher than normal iron levels were observed in the gut and the liver, especially in the iron-deficient supplemented group.

Daily-supplemented rats maintained a high mucosal iron content continuously, whereas the every-3-day supplemented rats had a lower iron content even the day after the iron supplement was ingested, which declined especially by day 3. This same pattern was observed in the proximal and distal jejunum and in the proximal ileum and was particularly clear in the distal ileum, where mucosal iron declined to the levels observed in normal animals.

In terms of liver nonheme iron, two distinct phenomena were observed. First, daily-supplemented iron-normal rats exhibited a gradual increment to reach levels that were threefold higher than normal and stabilized at those levels, whereas daily-supplemented iron-deficient rats exhibited a very rapid rise in nonheme liver iron, which in 2 days of supplementation had already reached normal mean levels or even higher. From then on, iron levels rose slowly but continuously throughout the 16–18 days of supplementa-

tion, reaching average levels four times higher than normal. Second, in the every-3-days supplemented rats, nonheme liver iron never reached more than 2.5 times normal levels and, again, showed a declining tendency during the two nonsupplemented days before the next scheduled dose, particularly in the iron-deficient supplemented group.

### Summary of Results of Daily and Intermittent Iron Supplementation in Preschool Children, Women of Childbearing Age, and Pregnant Women

#### Preschool Children

Because of the very promising results in the experimental animals regarding the efficiency and safety of intermittent iron supplementation, Liu et al.<sup>60</sup> proceeded to study 246 healthy 3–6-year-old children in a kindergarten in the city of Changji, Xinjiang Province, People's Republic of China. Thirty-seven percent of the children presented with Hb levels below 110 g/L. All of the children were distributed by age into nine classrooms, three for each age group. Each of the three age-determined classrooms was randomly assigned to either a daily (group 1), biweekly (group 2), or weekly (group 3) iron supplementation regimen that provided the children with 6 mg elemental iron/kg/dose under direct supervision. This is a therapeutic level of iron for small children and is equivalent to supplementing adult women with 120 mg elemental iron (close to 10 times the normal intake).

Growth, hemoglobin, and serum ferritin concentrations were measured before and after 3 months of supplementation. Any child with a health problem was reported that day to the kindergarten clinic by the child-care nurses who cared for the children 8 hours each day 6 days per week. These nurses did not know the purpose of the study or the content of the tablets.

The hemoglobin and ferritin results are summarized in Table 3, where children were grouped by their initial hemoglobin level as either anemic (Hb < 110 g/L) or nonanemic. The arithmetic mean of hemoglobin and the geometric mean of plasma ferritin are presented.

All of the anemic children responded to the three supplementation regimens with an increase of 10 g Hb/L or more, and 31% of the nonanemics also increased their hemoglobin levels by at least that much. Among the nonresponders there was a mild regression to the mean. Serum ferritin levels among the anemic children in group 1 reached concentrations as high as 1.85 times the highest initial values among nonanemic nonresponders (considered iron sufficient), whereas values in group 3 were superimposable on those in the latter group. Group 2 was intermediate (Figure 2). Serum ferritin concentrations among the nonanemic children rose only modestly, not reaching the elevated values observed in the anemic children.

**Table 3.** Hemoglobin and Ferritin Levels in Preschool Chinese Children Receiving Daily, Biweekly, and Weekly Iron Supplements

Group Supplement Administration	Anemic Children					
	Anemics (n)		Mean Hemoglobin (g/L)		Serum Ferritin (µg/L)	
	Before	After	Before	After	Before	After
Daily	37	0	98.2 <sup>a</sup>	132 <sup>b</sup>	13.1 <sup>a</sup>	55.2 <sup>b,c</sup>
Biweekly	27	0	99.4	130	12.8	48.1 <sup>c</sup>
Weekly	30	0	100.0	127	12.1	26.7 <sup>c</sup>

Group Supplement Administration	Nonanemic Children					
	Nonanemics (n)		Mean Hemoglobin (g/L)		Serum Ferritin (µg/L)	
	Before	After	Before	After	Before	After
Daily	53	53	127	136	30.8	38.7
Biweekly	45	45	125	133 <sup>c</sup>	29.7	39.0
Weekly	52	52	128	136	28.9	33.6 <sup>c</sup>

<sup>a</sup> All values in anemic children are different from those in nonanemic children.

<sup>b</sup> All after values are different from all before values.

<sup>c</sup> Values differ from other after values within the same class.

The differences in side effects were dramatic. Among the children receiving daily doses, 35.4% and 39.7% of anemics and nonanemics, respectively, had side effects (anorexia, nausea, occasional vomiting, diarrhea, constipation, and abdominal discomfort). Among the children receiving twice-weekly doses, only 7.4% of anemics and 6.6% of nonanemics had side effects. Among the anemic and nonanemic children receiving weekly doses, 0% and 5.7%, respectively, had side effects.

We interpret these findings as follows: The amount of iron absorbed by these children from a weekly dose of 6 mg/kg was not only safe, based on serum ferritin levels, but also well tolerated and effective enough to prevent and even correct iron deficiency, bringing iron reserves to the level observed in non-iron-deficient healthy Chinese children and correcting mild to moderate anemia in the course of 3 months.

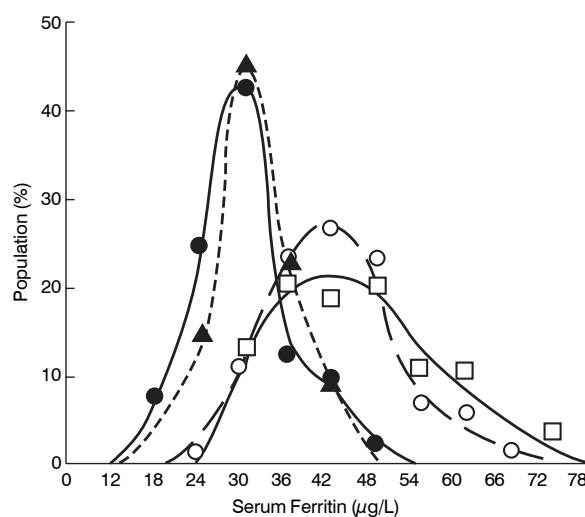
A study of anemic Indonesian preschool children also showed that a twice-weekly iron dose of 30 mg for 8 weeks was as effective as a 30 mg daily dose in correcting anemia.<sup>57</sup>

### Women of Childbearing Age

WHO<sup>13,28</sup> has recommended a daily regimen of 60 mg iron for 3 months a year (90 tablets/year) as a preventive/corrective strategy for iron deficiency and anemia in fertile-age women in populations where these conditions are highly prevalent. Instead of this schedule, within the concept of preventive supplementation, we propose here a community-based, long-term weekly supplementation schedule consisting of the intake of 60 mg iron throughout the year as a viable strategy.

In a study conducted in Berkeley, California,<sup>58</sup> these regimens were evaluated against a control group for their ability to prevent iron deficiency and anemia, correct mild to moderate forms of the latter, and increase iron reserves

in menstruating women 18–45 years of age. The study consisted of a double-blind trial involving two phases. In phase I, all participants received two bottles with tablets; they were instructed to ingest one tablet daily for 6 days from a larger bottle (containing more tablets) and one tablet weekly from a smaller bottle. During this phase, which lasted 3 months, women were asked to take the tablets between meals, or preferably before going to bed 2 or more hours after dinner. They were asked also to keep a diary of tablet intake and of any health problems or symptoms they experienced and to return the bottles with the remaining tablets at the end of 3 months. In phase II, all participants



**Figure 2.** Distributions, by serum ferritin levels, of previously iron-deficient preschool Chinese children receiving daily (open squares and solid line), twice-weekly (open circles and dashed line), or weekly (solid triangles and dashed line) iron supplements (6 mg/kg), compared with those of iron-normal preschool Chinese children (solid circles and solid line). Reproduced with permission from reference 56.

**Table 4.** Hemoglobin and Plasma Ferritin Values in Women of Childbearing Age Receiving Iron Supplements Daily for 3 Months, Weekly for 7 Months, or No Iron (see text)

Group	n	Hemoglobin (g/L)			Plasma Ferritin (µg/L)		
		Basal	3 months	7 months	Basal	3 months	7 months
1	37	134.0 <sup>a</sup>	137.5	137.5	28.4	43.2 <sup>a,b</sup>	29.6
2	35	136.1	136.5	139.9 <sup>a</sup>	31.6	31.9	34.8 <sup>c</sup>
3	44	134.7	135.8	138.7 <sup>c</sup>	35.8	32.8	32.4

<sup>a</sup> Significantly different from the other two values within the same group.

<sup>b</sup> Significantly different from all other plasma ferritin values.

<sup>c</sup> Significantly different from basal value within the same group.

took only a weekly tablet for 4 months without supervision and kept the same records as in phase I. Hemoglobin, zinc erythrocyte protoporphyrins, and plasma ferritin were evaluated at 0, 3, and 7 months.

Women were randomly assigned to one of three groups. In group 1 (daily iron for 3 months), the tablets in both bottles in phase I had 0.25 mg folic acid and 60 mg Fe as FeSO<sub>4</sub>, and only folic acid (0.25 mg) in phase II. In group 2 (weekly iron for 7 months), in phase I the larger bottle had only folic acid tablets (0.25 mg) and the smaller bottle had iron (60 mg) plus folic acid (0.25 mg). During phase II, the weekly tablet again contained both folic acid and iron. In group 3 (no iron supplement; control), all tablets in both phases contained only 0.25 mg folic acid. Of the 224 women recruited for the study, 116 participants completed it. The only difference between those who dropped out and those who continued in the study was that the dropouts were younger. Side effects were referred to as the cause for dropping out in 34%, 18%, and 4% of women in groups 1, 2, and 3, respectively.

At baseline 16% of the women were iron deficient on the basis of high zinc erythrocyte protoporphyrins and low plasma ferritins and 8% were anemic (Hb < 120 g/L). At the end of phase I there were no anemic women left in groups 1 and 2 and the proportion of anemics in group 3 also declined (regression to the mean). At the end of phase II only group 2 remained without anemic women. Table 4 shows the mean and standard deviation of Hb and the geometric mean and range of plasma ferritin levels.

Both iron-supplemented groups were equally efficient in bringing Hb levels above 120 or 125 g/L in 3 months, thus correcting mild to moderate ferropenic anemia. However, among the women receiving daily iron for 3 months but no more iron for 4 months (group 1), the proportion that at the end of the study had Hb values <125 g/L was the same as at the basal evaluation. In contrast, there were no women with Hb levels <125 g/L among women who continued weekly iron supplementation during those extra 4 months. This is the cutoff value for fertile-age women suggested by Viteri et al.<sup>59</sup> on the basis of a nutritionally normal Central American population.

The women receiving daily iron for 3 months (90 tablets) increased their plasma ferritin values by 15 mg/L, but

only temporarily, because these values fell to presupplementation levels in the following 4 months. It is important to note that the blood samples were obtained 5–7 days after the last iron dose to avoid a fictitious elevation from the recent intake of iron. In contrast, the women receiving weekly iron for 7 months (30 tablets) exhibited a progressive and sustained rise in plasma ferritin levels. This more physiological improvement in iron status strongly suggests a progressive enhancement of iron reserves that is consistent with the fact that all of these women retained Hb levels above 125 g/L.

The significant elevation of plasma ferritin at the end of 3 months of daily supplementation followed by a fall of similar magnitude (the shape of which we do not know) 4 months after having discontinued the supplementation suggests either of the following possibilities. First, the observed elevation may not reflect “true iron stores” but, rather, another metabolic condition induced by daily supplementation with iron for 3 months. This could be explained by an increase in apoferritin as a consequence of daily iron intake not necessarily associated with increased iron reserves. Second, the rapid increment in iron stores may be accompanied by a subsequent increase in iron losses, as has been observed in short intervention studies.<sup>60,61</sup> This phenomenon was also observed among daily iron-supplemented rats in contrast to every-3-day supplemented rats.<sup>48</sup>

### Pregnant Women

In a study by Liu et al.<sup>62</sup> primigravida pregnant volunteers, all older than 20 years of age and under antenatal care at Chang-ji Hospital, Xinjiang Province, China, were initially randomly assigned upon their first antenatal visit to one of three groups supplemented with iron plus folic acid tablets containing 300 g FeSO<sub>4</sub> (60 mg elemental iron) plus 0.25 mg folic acid. The tablets were administered under direct supervision, ideally between meals, by specially hired health workers. Group 1 (*n* = 64) received one tablet daily. Group 2 (*n* = 56) received two tablets together, also daily. Group 3 (*n* = 117) received two tablets together on a weekly schedule. By mid-study the word had spread among the women attending the antenatal clinic that women receiving weekly iron suffered essentially no side effects, and from then on,

**Table 5.** Hemoglobin and Plasma Ferritin, and Percent Anemia in Pregnant Chinese Women Receiving Daily or Weekly Iron Supplements or No Iron (see text)

Group	Hemoglobin (g/L)		Anemic (%)		Plasma Ferritin (µg/L)	
	Basal	Final	Basal	Final	Basal	Final
1	113.5	114.5	39	22 <sup>a</sup>	35	30
2	111.0	117.3	45	28	33	34
3	112.2	116.4	41	18	34	28
4	113.2	106.1 <sup>a</sup>	27	53 <sup>b</sup>	34	19 <sup>b</sup>

<sup>a</sup> All final values are significantly different from basal values.

<sup>b</sup> Significantly different from basal value and from final values in the other groups.

many women refused to enter the daily groups but were willing to take the weekly tablets. The number of women in group 3 was larger because in order to recruit the desired number of women in the other groups, we continued to receive a larger number of women in the weekly schedule. A negative control group, group 4 ( $n = 51$ ), received a placebo tablet weekly. The control group consisted of women who indicated they preferred not to receive iron but who accepted one weekly tablet containing  $\text{Na}_2\text{CO}_3$  usually prescribed to pregnant women if they complain of heartburn. This was (and is) an accepted practice by Xinjiang health authorities unless Hb levels become lower than 80 g/L, when women must receive treatment with daily iron plus folic acid (120 mg elemental iron plus 0.5 mg folic acid).

The first visit occurred at gestational weeks 13–26, when Hb was measured and supplementation was started. Plasma ferritin was also measured in a random subsample in each group at that time. A second blood specimen for the same determinations was obtained at 38 weeks of pregnancy or during labor at Chang-ji Hospital. These women were supplemented a median of 21 weeks, and no woman received less than 12 weeks of supplementation. There were no differences in the number of supplementation weeks between groups. The main findings of this study are presented in Table 5.

The lowest Hb value at term in all the groups supplemented with iron and folic acid was 92 g/L. In the “placebo” group all Hb levels at term were above 84 g/L. The percentage of women who complained of nausea and vomiting and the percentage who rejected continued ingestion of the tablets during the supplementation period is as follows: group 1, 17% had nausea and 10% ( $n = 7$ ) stopped ingestion; group 2, 46%/19% ( $n = 13$ ); group 3, 6%/0%; and group 4, 4%/0%.

The results from this study indicate that in this setting, weekly supplementation with 120 mg elemental iron to pregnant women for more than 12 weeks was as effective in terms of Hb and plasma ferritin levels at term as the two daily doses tested, and superior to group 4, which received no iron supplements. Weekly supplementation was also better than the daily schedule in that side effects

were minimal and there were no rejections.

A similar study was carried out in 301 women receiving antenatal care at a health center in a marginal area in Guatemala City by Chew et al.<sup>63</sup> The supplementation doses studied were 60 mg elemental iron daily and 180 mg weekly under supervised and unsupervised administration. Results indicate that daily iron supplementation is slightly better than weekly supplementation, but most of the differences in Hb and plasma ferritin levels at term are not statistically or biologically significant. The population in this study differed from that in the China study: in Guatemala, 27% of the pregnant women were below the age of 20 years and the median woman was in her fourth pregnancy. Anemia prevalence at term was 16% for the daily-supplemented group and 25% for the weekly-supplemented group. Hb at term was also measured in a “usual care” group of 82 women at the same health center. These women’s Hb levels were lower than those in both experimental groups, and anemia prevalence was 33%. A smaller number of women were motivated to ingest the daily ( $n = 26$ ) or weekly supplements ( $n = 14$ ) without supervision. Results in terms of Hb and plasma ferritin in these groups were no different from those in the supervised groups.

In those who were anemic at baseline, Hb rose 13.1 and 9.6 g/L in the daily and weekly groups. In nonanemics at baseline, Hb rose 1.8 g/L in the daily group and did not change in the weekly group. Overall, teenagers had significantly lower Hb initially and at term. Side effects were reported six to eight times more frequently in the daily than in the weekly group, but rejections because of side effects were not observed in this population.

Multiple regression analyses of the Chinese and the Guatemalan studies also yield different results. In China, the only variable that predicts Hb at term is initial Hb. The supplementation dose and schedule, the duration of supplementation, and the total supplemental iron intake are not significant predictors. In Guatemala, however, the logarithm of total supplemental iron intake is a significant predictor ( $\text{Hb at term} = 4.74 + 0.39 \text{ initial Hb} + 0.35 \ln \text{ total supplemental iron}$ ), but the magnitude of its influence on Hb at term is low compared with the influence exercised by the initial Hb. These two studies clearly point out that iron

nutritional status and Hb level at the beginning of pregnancy are the most important factors in preventing anemia at term among supplemented women. They also demonstrate that there are no important differences in the efficacy of daily and weekly iron in pregnancy in these populations. An important benefit of the weekly schedule in both studies is the lower rate of side effects and, in China, a much lower rate of rejections to iron supplementation.

### Studies on Absorption of Daily and Weekly Doses of Iron

There is controversy on whether in humans there is a blocking effect of previous doses of iron, as has been demonstrated in several animal species. This has led to doubts about the basic hypothesis that more efficient iron absorption could be achieved if iron were administered in synchrony with intestinal mucosal turnover in humans.

Cook and Reddy<sup>64</sup> explored the hypothesis that 50 mg iron administered weekly is absorbed better than the same dose administered daily in a 1-week study comprising essentially iron-normal subjects in Kansas City. They found that the weekly dose was absorbed 13% better than the daily dose, although if an aberrant case is eliminated, the increment in absorption of the weekly dose is near 30%.<sup>65</sup> This paper has provoked an exchange of letters to the editor<sup>66,67</sup> presenting different points of view on this study.

We are conducting a 5-week-long study according to a published protocol<sup>68</sup> that includes two populations: one in Berkeley, California, where we have selected close to 30% iron-deficient and mildly anemic adult volunteers, and another in Senegal, where the subjects are moderately anemic owing to iron deficiency. The objective is to determine whether the difference in iron absorption rates in response to daily and every-3-days supplementation observed between iron-deficient and iron-normal rats also occurs in humans.

A most important result is that among iron-deficient anemic subjects we have observed iron absorptions as high as 55% of a 60 mg dose, which means that 33 mg iron have been absorbed. This is equivalent to 4.7 mg iron daily if the dose is administered on a weekly basis. This amount of iron is sufficient to cause replenishment of iron reserves if they are exhausted and to induce a reasonable rate of recovery in moderately anemic subjects. Similar amounts of absorbed iron have been observed among iron-deficient and anemic subjects in studies in Europe and the United States.<sup>64,69-71</sup> It is still too early to answer the question we posed in our study.

### Conclusions

Iron supplementation of pregnant women is a common strategy to control iron deficiency in most of the developing world. Unfortunately, supplementation has proven to be ineffective for a variety of reasons in the great majority of

instances in populations most in need. An important reason for its lack of effectiveness is poor adherence and, worse, rejection of the daily intake of large doses of iron because of undesirable side effects.

Studies in iron-deficient animals have suggested that the administration of intermittent iron supplements in synchrony with intestinal mucosal turnover substantially improves the efficiency of iron absorption and retention, compared with daily supplementation. The magnitude of this phenomenon in iron-deficient humans still needs to be measured.

Field and clinical trials in preschool-age children, adolescent girls, women of childbearing age, and pregnant women have demonstrated the efficacy of weekly iron supplementation compared with daily supplementation in improving iron nutrition, including the progressive elevation of iron reserves and even the correction of mild to moderate ferropenic anemia.

These studies have also demonstrated that the weekly doses are almost free of side effects, in contrast to the daily doses, which are accompanied by side effects and by plasma ferritin elevations that appear higher than levels observed in iron-sufficient populations. This may be undesirable.

A few studies in school-age children, women of childbearing age, and pregnant women where supplementation has been school- or community-based are also beginning to show that weekly iron supplementation is effective in controlling (preventing and correcting) iron deficiency. Longer-term community-based (phase II) studies under "field conditions typical of programs" are urgently needed to evaluate the sustainability of this approach as well as long-term compliance.

The information available also suggests that community-based weekly preventive iron supplementation to provide fertile-age women (and adolescents where teenage pregnancies are common) with iron reserves and to prevent iron deficiency in infancy can be effective under field conditions.

The results from iron supplementation programs for pregnant women suggest strongly that the most important factor in determining Hb concentration at term is the Hb level in the initial evaluation. Initial ferritin levels also correlate with Hb at term. Preliminary findings of iron absorption in anemic iron-deficient subjects are yielding absorption rates as high as 50% with doses of 60 mg elemental iron and as high as 30% with doses of 120 mg. These results support the efficacy observed in the weekly supplementation field trials.

*Note:* Since this paper was prepared, a paper by Ridwan et al.<sup>72</sup> and an editorial by Yip<sup>73</sup> have appeared. Ridwan et al.'s paper indicates that in Indonesian pregnant women there are no differences between daily and weekly supplementation in a community setting for an average of 11 weeks. Unfortunately, the supplementation period was

short and adherence to the supplementation was rather poor, particularly among women with side effects (where there were a greater number among the daily group). The end result of this study is rather disappointing for both daily and weekly doses. Viteri<sup>74</sup> wrote a letter to the editor emphasizing the need to consider pregnancy as an event that is part of the reproductive cycle of women. This cycle, as proposed in the concept of preventive supplementation, starts before pregnancy to raise iron reserves in fertile-age women, covers pregnancy, and continues through breast-feeding or through the interpartum period. To consider pregnancy as an isolated event in terms of a woman's life and particularly in terms of iron nutrition, as we have done until now, is a serious mistake in our thinking.

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