

# Iron requirements in pregnancy and strategies to meet them<sup>1-3</sup>

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**ABSTRACT** Iron requirements are greater in pregnancy than in the nonpregnant state. Although iron requirements are reduced in the first trimester because of the absence of menstruation, they rise steadily thereafter; the total requirement of a 55-kg woman is  $\approx 1000$  mg. Translated into daily needs, the requirement is  $\approx 0.8$  mg Fe in the first trimester, between 4 and 5 mg in the second trimester, and  $>6$  mg in the third trimester. Absorptive behavior changes accordingly: a reduction in iron absorption in the first trimester is followed by a progressive rise in absorption throughout the remainder of pregnancy. The amounts that can be absorbed from even an optimal diet, however, are less than the iron requirements in later pregnancy and a woman must enter pregnancy with iron stores of  $\geq 300$  mg if she is to meet her requirements fully. This is more than most women possess, especially in developing countries. Results of controlled studies indicate that the deficit can be met by supplementation, but inadequacies in health care delivery systems have limited the effectiveness of larger-scale interventions. Attempts to improve compliance include the use of a supplement of ferrous sulfate in a hydrocolloid matrix (gastric delivery system, or GDS) and the use of intermittent supplementation. Another approach is intermittent, preventive supplementation aimed at improving the iron status of all women of childbearing age. Like all supplementation strategies, however, this approach has the drawback of depending on delivery systems and good compliance. On a long-term basis, iron fortification offers the most cost-effective option for the future. *Am J Clin Nutr* 2000;72(suppl):257S-64S.

**KEY WORDS** Iron, requirements, absorption, pregnancy, strategies, therapy, women, iron fortification

## INTRODUCTION

The overall iron requirement during pregnancy is significantly greater than that in the nonpregnant state despite the temporary respite from iron losses incurred during menstruation. Iron requirements increase notably during the second half of pregnancy because of the expansion of the red blood cell mass and the transfer of increasing amounts of iron to both the growing fetus and the placental structures. Iron is also lost in maternal blood and lochia at parturition. The degree to which these increased requirements can be met depends on the size of iron stores at the start of pregnancy and on the amounts of dietary iron that can be absorbed during pregnancy. The fact that iron deficiency anemia frequently develops in pregnancy indicates that the physiologic adaptations are often insufficient to meet the

increased requirements. As a result, iron supplementation during pregnancy is a common practice throughout the world.

In the discussion that follows, 4 topics are addressed. The first covers the nature and extent of iron requirements during the 3 trimesters of pregnancy. The second describes iron balance in pregnancy, including the adaptive changes that occur in iron absorption during pregnancy. The third discusses assessing iron status during pregnancy, and the last reviews the various supplementation strategies that have been used to combat iron deficiency during pregnancy.

## IRON REQUIREMENTS DURING PREGNANCY

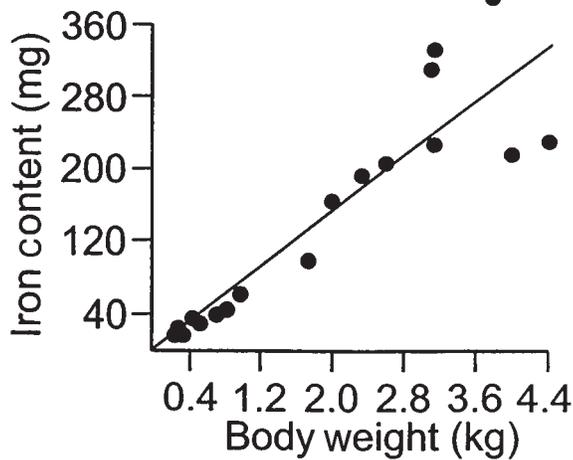
If the demand for iron were spread evenly throughout gestation, iron requirements could be met more easily by a sustained rise in the rate of iron absorption. The need for iron, however, varies markedly during each trimester of pregnancy. Iron requirements decrease during the first trimester because menstruation stops, which represents a median saving of 0.56 mg Fe/d (160 mg/pregnancy) (1). The only iron losses that must be met during this period are the obligatory ones from the body via the gut, skin, and urine, which amount to  $\approx 0.8$  mg/d in a 55-kg woman ( $14 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$  or 230 mg/pregnancy) (2). Early hemodynamic changes include generalized vasodilation, some increase in the plasma volume, and an increase in red blood cell 2,3-diphosphoglycerate concentrations (3, 4). There is also some evidence that erythropoietic activity may be reduced during this period, with a slight reduction in red blood cell mass (5), a reduction in the number of reticulocytes (4), and a rise in the serum ferritin concentration (4, 6).

During the second trimester, iron requirements begin to increase and continue to do so throughout the remainder of pregnancy. The increase in oxygen consumption by both mother and fetus is associated with major hematologic changes. Most studies in women supplemented with iron show a change in total blood volume of  $\approx 45\%$ , with an increase in plasma volume of  $\approx 50\%$  and an increase in red blood cell mass of  $\approx 35\%$  (7). The rise in hemoglobin mass is similar at  $\approx 30\%$  (8). There has been some

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**FIGURE 1.** Relation between body weight and body iron content in the fetus and newborn child (10).

difficulty in establishing the normal hemoglobin concentration in pregnancy because of both the disproportionate increases in the plasma volume and the frequent occurrence of iron deficiency anemia. In studies in which iron deficiency was prevented, however, the average decrease in hemoglobin concentration appeared to be  $<10$  g/L (7, 9). Translated into iron requirements, the increase in red blood cell mass that occurs in a normal pregnancy amounts to  $\approx 450$  mg Fe in a 55-kg woman (8). Whereas this represents a significant drain during the later part of the pregnancy, it does not affect long-term iron balance because the iron is returned to the body's stores at the end of pregnancy, when the red blood cell volume gradually reverts to normal.

As pregnancy progresses, iron requirements for fetal growth rise steadily in proportion to the weight of the fetus, with most of the iron accumulating during the third trimester (10; **Figure 1**). The average iron content of a fetus weighing  $>3$  kg is  $\approx 270$  mg (10).

In determining iron requirements during pregnancy, the losses incurred during parturition must also be added. These include an average maternal blood loss equivalent to 150 mg Fe and a further 90 mg present in the placenta and umbilical cord (7). In the period after delivery, there is a small additional iron loss of  $\approx 0.3$  mg/d through lactation (11), but this is offset by the absence of menstruation, except when breast-feeding is continued long after the return of menstruation.

In summary, the total iron requirement during pregnancy for a 55-kg woman is  $\approx 1040$  mg (**Table 1**). At delivery, there is a further loss of maternal blood, which raises the total cost of pregnancy to  $\approx 1190$  mg iron. The net cost, however, is only 580 mg because the iron used to increase the red blood cell mass is returned to stores and overall losses are further offset by the absence of menstruation during pregnancy.

### IRON BALANCE IN PREGNANCY

When total iron requirements during pregnancy are translated into increased daily needs, it is apparent that there is an unequal distribution over time (**Figure 2**). Although reduced during the first trimester, iron requirements rise to between 4 and 6 mg in the second and third trimesters, respectively (12). Because major

changes in the red blood cell mass start occurring only in the middle of the second trimester (4, 13), iron requirements may reach as much as 10 mg/d during the last 6–8 wk of pregnancy (14). Irrespective of the exact value, it is apparent that daily iron requirements cannot be met from dietary absorption alone in the latter part of pregnancy, even from the most optimal diet (7). In diets containing large quantities of bioavailable iron—diets in which there are generous quantities of meat, poultry, fish, and foods containing high amounts of ascorbic acid—overall iron absorption is usually 3–4 mg/d and, at most, 5 mg/d (4). The amount of iron absorbed is much lower when the diet contains only small amounts of bioavailable iron (4, 12), as is often the case in many developing countries where the staple food is cereal and the intake of meat and ascorbic acid is limited.

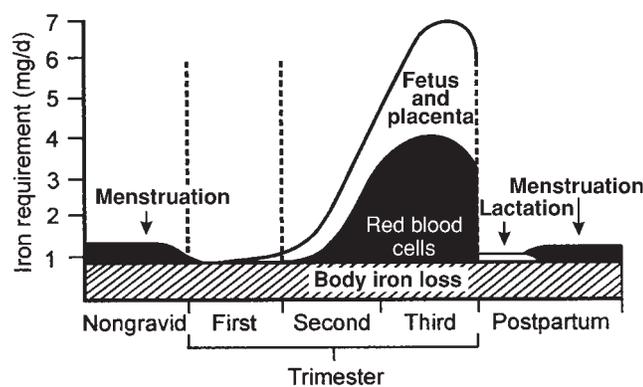
### Importance of iron stores

From the preceding discussion, it is apparent that iron balance can be maintained in pregnancy only when there are adequate iron stores at the start of pregnancy. If a woman routinely eats a diet high in bioavailable iron, a prepregnancy iron store of 300 mg is probably sufficient to carry her through pregnancy, although a higher amount of stored iron is needed when the diet is less than optimal.

The extent to which women of reproductive age can meet their iron requirements during pregnancy has been estimated from studies that calculated iron stores through measurements of serum ferritin concentrations and other hematologic indexes, with use of the equation developed by Cook et al (15). In the original study, which was carried out in women in the Pacific Northwest of the United States, calculated median iron stores were  $\approx 300$  mg and  $\approx 20\%$  of the women had no iron stores at all (15). Lower but virtually identical results were obtained from the second National Health and Nutrition Examination Survey data and from a Swedish study (14), in which the calculated median amount of iron stored was 150 mg and only 20% of women had iron stores  $>250$  mg. In a group of teenagers aged  $>15$  y, the calculated median value was even lower at 70 mg (14). In a random sample of Australian girls, living in a country where meat consumption is high, iron stores were calculated to be  $>200$  mg (14, 16). Although data do not exist to enable similar calculations for women in developing countries, the high prevalence of low serum ferritin concentrations and overt iron deficiency anemia in

**TABLE 1**  
Iron requirements in pregnancy

	Amount
	<i>mg</i>
Total cost of pregnancy	
Fetus	270
Placenta	90
Expansion of red blood cell mass	450
Obligatory basal losses	230
Sum	1040
Maternal blood loss at delivery	150
Total cost	1190
Net cost of pregnancy	
Contraction of maternal red blood cell mass	−450
Absence of menstruation during pregnancy	−160
Subtotal	−610
Net cost	580



**FIGURE 2.** Estimated daily iron requirements during pregnancy in a 55-kg woman. Modified from Bothwell et al (7) with permission.

these populations indicate that a large proportion of the women enter pregnancy with little or no iron stores (17).

### Iron absorption at different stages of pregnancy

Studies with radioactive and stable isotope of iron have provided insights into the changes that occur in iron absorption during pregnancy. The studies can be divided into those in which the absorption of nonheme iron from different mixed diets was measured and those in which the absorption of various doses of inorganic iron was measured. The amount of iron absorbed in each of the studies differed because of variations in the iron dose and regimen. Nevertheless, the overall pattern was remarkably similar, with a progressive rise in iron absorption as pregnancy advanced.

There is, however, some evidence that iron absorption decreases during early pregnancy, probably because of lower iron requirements. In women who were to undergo legal abortion and who were fed a test meal in early pregnancy, iron absorption was only 2.5% compared with 12.6% at 2 mo after the pregnancy was terminated; comparable figures for a 3-mg dose of ferrous iron fed in the fasting state were 10% and 42.6%, respectively (18). In another study, the median iron absorption from a mixed meal was only 0.7% in the first trimester compared with 4.5% at 24 wk, 13.5% at 36 wk, and 6.5% at 8–10 wk after delivery (19). The relatively low values for iron absorption were ascribed to the meal's containing several iron absorption inhibitors. At the same time, the contribution of heme iron to overall iron absorption was not measured. In this context, it is noteworthy that the median amount of nonheme iron absorbed during early pregnancy was 3 times greater when a highly iron-bioavailable hamburger meal was eaten (18). Through the use of values for iron absorption during each trimester of pregnancy, total iron absorption (heme and nonheme) from a highly bioavailable diet containing adequate amounts of meat and ascorbic acid was calculated to be 0.4, 1.9, and 5.0 mg in the first, second, and third trimesters of pregnancy, respectively (4). Proportionately smaller amounts of iron would be absorbed from diets with a lower bioavailability, which is the case for most pregnant women in developing countries.

Further insights into the patterns of iron absorption in pregnancy and the effects that might be anticipated from using different doses of supplemental iron were obtained from studies in which ferrous iron was administered. In fasting subjects fed a small dose of ferrous iron (0.56 mg), iron absorption was 30% at 8 wk of gestation. There was little change in iron absorption until

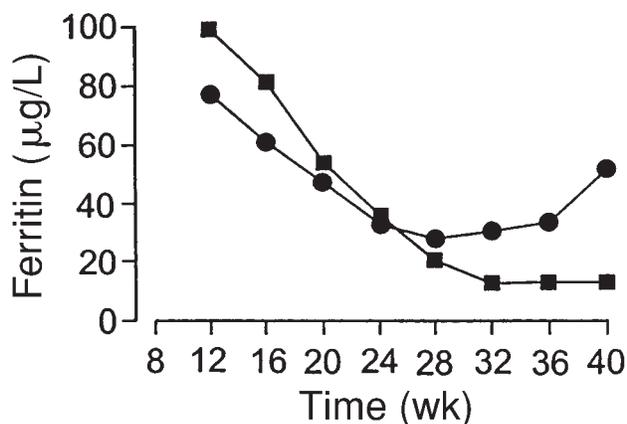
the 16th week, after which it began to rise steadily before reaching a plateau of  $\approx 90\%$  at 30 wk (20). The absorption rates for a 5-mg dose of iron were lower: 7.2%, 21.1%, 36.3%, and 26.3% at 12, 24, and 36 wk of gestation and at 12 wk postpartum, respectively (21). Increasing the dose of ferrous iron to 100 mg lowered the absorption rates even further to 6.5%, 9.2%, 14.3%, and 11.1% at 12, 24, and 35 wk of gestation and at 8–10 wk postpartum, respectively (22).

The main conclusions that can be drawn from the above studies are that iron absorption decreases during the first trimester of pregnancy, rises during the second, and continues to increase throughout the remainder of pregnancy. Iron absorption remains elevated during the first months after delivery, which allows for some reconstitution of body iron stores.

### ASSESSMENT OF IRON STATUS IN PREGNANCY

Assessing iron status during pregnancy is fraught with difficulties because the profound hemodynamic changes associated with pregnancy affect several indexes of iron status. During pregnancy, hemodilution leads to a reduced hemoglobin concentration, whereas both serum iron and ferritin concentrations decrease and total iron-binding capacity increases (8, 22, 23). The relative contributions of pregnancy per se and a pregnancy-induced negative iron balance in bringing about these changes can be assessed by measuring the changes in hemoglobin, serum iron, serum ferritin, and total iron-binding capacity that occur during pregnancy in women rendered iron replete after adequate iron supplementation during pregnancy (8, 22, 23).

The disproportionate increase in plasma volume during pregnancy leads to a drop in the hemoglobin concentration of  $\approx 10$  g/L (7). Although hemoglobin concentrations  $< 110$  g/L have been occasionally reported in iron-replete women (8), this concentration has proved to be a useful cutoff for defining anemia in pregnancy (12). There is a moderate drop in the concentration of serum iron that stabilizes in the middle of pregnancy (22). More dramatic than the changes in either hemoglobin or serum iron concentrations is the steady rise in total iron-binding capacity during pregnancy to  $\approx 50\%$  above normal, which reflects an increase in the concentration of transferrin in plasma (22). As a result, there is a drop in transferrin saturation. As discussed previously, there is some evidence that serum ferritin



**FIGURE 3.** Effects of iron supplementation on serum ferritin concentration in pregnancy. Supplemented group, ●; unsupplemented group, ■ (23).

rises modestly early in pregnancy, presumably because of reduced erythropoietic activity; thus, iron is diverted to stores (4, 6). Thereafter, however, the serum ferritin concentration drops steadily to  $\approx 50\%$  of normal at midterm (**Figure 3**) (23, 24). These changes reflect hemodilution and the mobilization of iron from stores to meet the increased demands of pregnancy.

It is, therefore, apparent that all the indexes associated with iron deficiency—including hemoglobin, transferrin saturation, and serum ferritin concentrations—are reduced during pregnancy even in iron-replete women. In contrast, the concentrations of circulating transferrin receptor have been found to be normal in pregnancy, only being raised if iron deficiency is present (25, 26). This suggests that serum transferrin receptor concentrations may prove to be a useful tool for diagnosing iron deficiency in pregnancy.

## STRATEGIES TO COMBAT IRON DEFICIENCY IN PREGNANCY

### Daily supplementation

Iron supplementation regimens in pregnancy vary depending on the characteristics of the population. In developed countries most women enter pregnancy with normal hemoglobin concentrations and variable amounts of stored iron. In contrast, large numbers of women in developing countries are anemic at the onset of pregnancy (17). Prenatal iron supplementation is not compulsory in many industrialized countries and the recommended dose is often small (30 mg ferrous iron daily), but has been as high as 240 mg/d in developing countries, for example, India (27). In 1989 the World Health Organization (WHO) recommended universal supplementation of all pregnant women with 60 mg ferrous iron twice daily in populations where gestational anemia is common and once daily in populations where overall iron nutrition is better (28). This recommendation was subsequently modified to a single daily dose of 60 mg Fe for 6 mo in pregnancy or 120 mg Fe if 6 mo duration cannot be achieved (29). Keeping the dose as low as is compatible with unimpaired effectiveness is an important principle because the side effects of iron therapy, which can seriously limit compliance, are dose-dependent phenomena (30).

Recommendations on the use of prenatal iron supplements need to be considered against the background of what is known about iron requirements and iron balance at the different stages of pregnancy. The iron requirement during pregnancy is, as discussed previously, between 800 and 1000 mg depending on the size of the woman (45–55 kg), with most of the extra requirements occurring in the second half of pregnancy. As was also discussed previously, iron absorption from a diet of very high iron bioavailability has been estimated to be 0.4, 1.9, and 5.0 mg/d during the first, second, and third trimesters, respectively (4). A diet with the above absorption rates would provide a total of 600 mg Fe during pregnancy, leaving a deficit of 200–400 mg Fe that would have to be met by mobilizing iron from stores, if they exist, and from the absorption of supplemental iron. In such circumstances, a daily dose of 30 mg ferrous iron during the second half of pregnancy would appear to be adequate because the daily absorption rate that would be required to make up the deficit would be at most  $\approx 10\%$ . This is, in fact, the iron dose widely used in developed countries, where it is given together with 250–400  $\mu\text{g}$  folic acid.

Although a low iron dose and a once-daily schedule are both positive factors in ensuring compliance, it is perhaps noteworthy that  $>30\%$  of low-income women in the United States are still anemic during the third trimester of pregnancy (31). The latter can probably be ascribed to both the consumption of a diet with relatively low iron bioavailability and poor compliance in taking iron supplements. Whether a dose larger than 30 mg of supplemental iron would reduce the prevalence of anemia is not clear, but note that in their classic study, de Leeuw et al (8) found that the mean hemoglobin mass at term was lower in women receiving 39 mg ferrous iron daily than in those receiving double that amount.

The problem of anemia during pregnancy in many developing countries is compounded by the fact that many women consume diets of low iron bioavailability and, therefore, enter pregnancy with no iron stores and less than optimal hemoglobin concentrations. In such circumstances, the iron deficit that must be met is correspondingly greater. During the latter part of pregnancy, between 200 and 400 mg Fe can be absorbed from diets with low to medium bioavailability; thus, a deficit of as much as 600–800 mg must be met from iron supplementation. The extra amounts of iron that would have to be absorbed to meet such a deficit would be 5.5–7 mg/d if supplementation was started at 20 wk of gestation, and double this concentration if it were started at 30 wk. These amounts could be met if 9–12% and 19–24% of a 60-mg ferrous iron tablet given in the fasting state at 20 and 30 wk of gestation, respectively, was absorbed. The above absorption ranges are not out of line with those obtained in radioiron studies using a 100-mg dose of ferrous iron (9.2% in the second trimester and 14.3% in the third trimester) (22). For optimal results, the iron must be administered between meals because food reduces the absorption of iron substantially (32).

From the above calculations, it is apparent that a daily dose of 60 mg ferrous iron given to fasting pregnant women throughout the second half of pregnancy should be sufficient to combat iron deficiency in developing countries. A dose of 120 mg/d should be required only when iron deficiency is a problem in women who are not pregnant or when supplementation therapy is not started the beginning of the second trimester (29, 33). However, a recent meta-analysis of the results from controlled studies raised questions about the optimal dose of iron supplementation. A daily dose of 60 mg Fe was associated with only a 2-g/L rise in the hemoglobin concentration compared with that of control subjects (34), whereas larger increases of 12 and 16 g/L were obtained with doses of 90 and 120 mg, respectively. These unexpected findings need to be confirmed because they appear to be at variance with the known relations between the dose of iron and the percentage absorbed (7, 8, 22).

Although virtually all well-controlled iron supplementation trials have shown a positive effect on status, in proportion to the dose and duration of iron therapy, there is little evidence that the results of such trials can be reproduced in national health care programs (34, 35). The latter is due to both biological and programmatic factors.

From the biological perspective, the etiology of anemia in developing countries is multifactorial and can be expected to vary by region and by season (36). In addition to the poor bioavailability of dietary iron, intestinal worm infections and particularly blood loss from hookworm infections compound the problem of anemia in many areas (37). Other important etiologic factors include folate deficiency (38); vitamin A deficiency (39);



a variety of infections, including malaria and HIV infection (40); and hemoglobinopathies (36, 38). HIV infection is particularly prevalent in sub-Saharan Africa and has been shown to be associated with a median hemoglobin decrease of 5.5 g/L in asymptomatic pregnant women (40).

Programmatically, several factors can limit the effectiveness of iron supplement interventions, including problems related to costs and logistics that affect the supply of iron tablets, poor access to prenatal care, insufficient counseling on the need for and benefits of iron supplementation, and an unwillingness by pregnant women to take iron supplements (35). Available literature from several countries suggests that the most important reason for the failure of supplementation programs is a lack of supplies (41), but noncompliance on the part of pregnant women can also be a significant factor (42). Noncompliance is the result of both an aversion to the side effects of taking iron supplements and the failure of many primary health care systems to adequately motivate both health care providers to issue the iron tablets and pregnant women to take them (41). The problem of noncompliance was highlighted in 2 studies. One study, in Tanzania, found only 42% of pregnant women adhered to a twice-daily schedule of 60 mg Fe as ferrous sulfate (43). In the other study, in Indonesia, 36% of the women who had been receiving 60 mg ferrous iron daily had positive results on stool tests for iron (44).

Various strategies have been adopted to reduce the gastrointestinal side effects associated with taking iron supplements, such as nausea and epigastric pain, which are important factors in noncompliance. Side effects are dose related (30); thus, a reduction in both the concentration and frequency of the oral iron dose has been advocated. As discussed previously, the minimum effective dose of iron for a woman entering pregnancy with no iron stores is 60 mg/d and may be even greater for those who are already anemic at the onset of pregnancy. An alternative approach would be to administer the iron in a form that is both well absorbed and likely to produce fewer side effects. In this context, a formulation referred to as a gastric delivery system (GDS) has proved particularly promising (45, 46). The GDS consists of ferrous sulfate incorporated into a hydrocolloid matrix that becomes buoyant on exposure to gastric secretions; thus, the GDS is retained for prolonged periods in a soluble form in the acidic environment of the stomach. Two trials have been conducted using the GDS and both showed that it is as effective as ferrous sulfate when given at half the dosage and that it is well tolerated (43, 46). Its widespread application could, however, still be bedeviled by the operational problems that beset so many iron supplementation programs. Indeed, these problems remain of such magnitude in parts of the Middle East that the United Nations Relief Works Agency recently recommended that routine universal prenatal iron supplementation be considered only in those countries where severe anemia is present and that most countries direct their attention to identifying and treating anemic subjects (47).

### **Intermittent iron supplementation therapy**

An alternative approach to daily iron supplementation therapy, be it for pregnant women or other individuals, is to give iron intermittently once or twice per week (33). The approach is based on experimental evidence that iron absorption is reduced in rats in the days immediately after the initial administration of a large dose of iron but is resumed after  $\approx 3$  d (48). It was therefore argued that the administration of iron weekly or twice

weekly would be both more rational and cost-effective with fewer side effects (33). The rationale of the approach is, however, dubious, because the results of several double-isotope studies in human subjects have not confirmed the presence of a mucosal block when oral iron is given daily (32, 49, 50), with the results of one study showing a 6-fold greater absorption with daily as compared with weekly iron therapy (32). Despite the spirited debate on both the rationale and efficacy of the approach (51–54), it has been widely applied in preschool children (55, 56), schoolchildren (57), female adolescents (58), and pregnant women (59), and the results of several other trials have been reported at scientific meetings and in abstracts and preliminary reports (41). In addition, several developing countries seem to be in the process of changing their prenatal iron supplementation policy from daily to intermittent supplementation (41).

The studies on intermittent iron supplementation that are of most immediate relevance to the present review are those conducted in pregnant women. In the one published study, which was carried out in West Java, hemoglobin concentrations rose significantly with both daily and weekly supplementation (59), but the increases were lower than reported in previous supplementation trials in which supervision was optimal (8, 22). Compliance was poor in both groups (59). The relative efficacy of intermittent iron supplementation in different situations has been put into clearer perspective 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 in Developing Countries: An Analysis of Experience. Final Report to the Micronutrient Initiative," April 1999, unpublished) who analyzed the data in 14 completed trials, many of which are not yet published. The final prevalence of anemia was greater with intermittent weekly therapy in each of the 4 trials conducted during pregnancy and it was concluded that weekly, instead of daily, iron administration is not recommended for pregnancy regardless of the degree of supervision that can be arranged. It was also noted that unless supplementation programs are tightly controlled they can be expected to have limited effectiveness.

Further insight into problems attendant on iron supplementation in pregnancy was recently obtained in a study in Bangladesh in which weekly and daily supplementation were compared (60). Compliance was monitored with an electronic counting device that recorded the dates and times when the pill bottle was opened. Ordinary least-squares regression analysis showed a dose response between iron and hemoglobin that did not differ between the groups. It was concluded that iron absorption was not improved in the weekly group and that daily iron supplementation was more effective than weekly because of the higher dosage of iron that it provided.

Intermittent iron supplementation therapy is also being applied to other iron-deficient groups, such as young children and women of childbearing age, with the aim of improving iron nutrition (55–58). The rationale for its use by women of reproductive age is for prevention, whereby the long-term application of intermittent therapy will ensure that women enter pregnancy with adequate iron reserves (33). Such a program of preventive supplementation is similar in aim to the WHO recommendation that supplemental iron be given to adolescents and women in vulnerable populations for 2–4 mo/y (28). Analysis of the data in 10 completed trials, both published and unpublished, in which intermittent iron therapy was given to children and adolescents, led Beaton and McCabe (unpublished observations, 1999) to



several general conclusions: "Weekly iron supplementation is likely to be less effective than daily administration, except in situations where supervision is feasible with weekly regimens but not with daily supplementation. Unless ways are found to improve 'compliance' greatly, in comparison to that seen in existing countries, neither daily nor weekly iron supplementation is likely to be an effective approach to preventing and controlling iron deficiency anemia in developing countries." Although there may well be a place for a more limited application of supervised weekly supplementation in some settings, such as through schools and the workplace, the current evidence suggests the need for more effective long-term strategies.

Two strategies that merit consideration are programs to modify dietary habits (61) and iron fortification of foods (62). The second has the advantage that it can be applied to large population groups at low cost and the identification and cooperation of deficient or potentially deficient individuals is not a prerequisite, as it is with supplementation. Although there are also problems associated with the implementation of iron fortification of foods, these are not insuperable and the results of 2 trials using iron-EDTA in developing countries have already indicated the potential impact of such programs (63, 64). Although none of the strategies for combating iron deficiency are mutually exclusive, iron fortification programs adapted to the dietary habits of different populations hold the promise of yielding the most cost-effective benefits in the long term. 

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## DISCUSSION

**Dr Martorell:** David Rush told us that anemia does not affect birth weight. I would qualify that and say that evidence from randomized controlled trials is not sufficient to answer the question. The impediment is ethical issues—because of the WHO recommendation that iron supplementation cannot be withheld from pregnant women. However, we should think beyond birth weight as an outcome because it is not the only, nor maybe the most sensitive, child outcome. Fetal iron stores and the prevention of anemia in children have all kinds of functional consequences. What do we know about, for example, iron supplementation in pregnancy and fetal stores and the prevention of anemia in infants?

**Dr Bothwell:** It is a muddy area and one that deserves more attention. In a carefully conducted early study, based on hemoglobin and hematocrit measurements, it was concluded that the fetus is able to obtain the iron it requires even if the mother is iron deficient [Sturgeon P. *Br J Haematol* 1959;5:31–55]. When serum ferritin was used as a measure of iron status, conflicting results were obtained, with some studies showing a correlation between maternal and fetal iron status and others not [Hallberg L. Iron balance in pregnancy and lactation. In: Foman SJ, Zlotkin S, eds. *Nutritional anemias*. New York: Raven Press, 1992:13–28;

Preziosi P, Prual A, Galan P, Daouda H, Boureima H, Herberg S. Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. *Am J Clin Nutr* 1997;66: 1178–82]. In the most recent study, there were no differences in cord blood iron measurements between an iron-supplemented and a placebo group, but anemia and a low serum ferritin were significantly more common in the placebo group at 3 and 6 mo [Preziosi et al]. This latter observation is potentially important, because the hematologic changes were occurring at a time of rapid growth and crucial brain development.

**Participant:** Could you clarify the statement that iron requirements for the woman are calculated by using data from different studies to ascertain the different components that determine requirements but not from studies of any ill effects, such as anemia?

**Dr Bothwell:** In a classic Canadian study conducted a number of years ago, de Leeuw and her colleagues [de Leeuw NKM, et al. *Medicine* 1966;45:291–315] gave pregnant women adequate iron supplements, either as parenteral or oral iron, and compared the findings with those in a control group who received no iron therapy. During the last trimester, iron treatment was associated with a higher hemoglobin, red cell mass, and serum iron concentration, whereas plasma volume changes were the same in both

groups. These results have subsequently been used as a yardstick to define the optimal hematologic response in pregnancy, where erythropoiesis is not compromised by an inadequate supply of iron. In passing, it is of interest that the serum erythropoietin rises in pregnancy, even in women receiving iron supplements [Milman N, Agger AO, Nielsen OJ. Iron status markers and serum erythropoietin in 120 mothers and newborn infants. Effect of iron supplementation in normal pregnancy. *Acta Obstet Gynecol Scand* 1994;73:200-4]. The fact that the degree of rise is inversely correlated with iron status markers suggests that the elevation reflects iron-deficient erythropoiesis.

