

Pregnancy and Iron Deficiency: Unresolved Issues

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Iron deficiency and iron deficiency anemia are prevalent among pregnant women. The extent to which iron deficiency affects maternal and neonatal health is uncertain. Existing data suggest that maternal iron deficiency anemia may be associated with adverse outcomes, including preterm delivery and higher maternal mortality. Further research is needed on the maternal and neonatal benefits of iron supplementation during pregnancy.

Introduction

Iron deficiency and subsequent iron deficiency anemia are the most prevalent nutrient deficiency problems afflicting pregnant women. The extent to which maternal iron deficiency affects maternal and neonatal health is still uncertain. This review describes the mostly circumstantial data suggesting that maternal anemia and/or iron deficiency may be associated with premature delivery and higher maternal mortality and possibly with lower pregnancy weight gain, poorer maternal immune status, lower birth weight, and changes in infant behavior. Despite a general assumption to the contrary, it is probable that maternal iron status during pregnancy affects infant iron stores at birth. However, these outcomes have not been evaluated systematically in randomized, prospective intervention trials that include a sufficient number of iron-deficient women, controlling for possible confounding factors. Thus, there is insufficient information to assess the overall adverse impact of anemia and iron deficiency during pregnancy. This uncertainty has led to controversy among agencies concerned about the importance and treatment of iron deficiency during pregnancy. Because of the very high prevalence of iron deficiency during pregnancy, and the circumstantial evidence of its detrimental effects on maternal and infant function, research to answer these questions is urgently needed.

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Prevalence

Iron deficiency and iron deficiency anemia are the most prevalent nutrient deficiency problems during pregnancy, and these conditions are more common in pregnant women than in any other population group. In developing countries, the prevalence of anemia in pregnancy averages 56%, ranging between 35% and 75% among different regions of the world.¹ The prevalence in developed countries is lower, but still substantial, averaging 18%. To put these prevalence rates in perspective, anemia also affects an average of 43% of nonpregnant women in developing countries and 12% in developed countries.¹ The prevalence of iron deficiency, which precedes anemia, is much higher. Even in industrialized countries, in the absence of iron supplementation average serum ferritin concentrations in late pregnancy fall into the deficient range.^{2–6}

Iron Metabolism During Pregnancy

Major changes in iron metabolism during pregnancy include the cessation of menses, expansion of the red blood cell mass by about 20%, and the deposition of substantial amounts of iron in the fetus and placenta. The expansion of maternal red cells is maximal around weeks 20–25 of gestation and is probably responsible for the marked fall in serum ferritin concentrations that occurs between about weeks 12 and 15. Most fetal iron uptake occurs after week 30, during a time when maternal serum ferritin is fairly constant. Thus, fetal and placental iron needs are presumably met predominantly by increased efficiency of maternal iron absorption during the last 10 weeks of pregnancy. Total circulating serum transferrin increases by about 250% between conception and term, probably in response to estrogenic hormones.⁷

Fetal iron is derived from maternal transferrin, which delivers iron to transferrin receptors on the apical surface of the placental syncytiotrophoblast (the layer of fused cells that separates the maternal and fetal circulations). Holotransferrin is endocytosed by these cells, and the apotransferrin is returned to the cell surface. The disassociated iron binds to ferritin in the placental cell, from which it is picked up by apotransferrin on the basolateral (fetal) surface

of the cells, and enters the fetal circulation as holotransferrin.⁸

The amount of iron transferred across the placenta depends on two factors: the number of transferrin receptors on the apical (maternal) side of placental cells, and the concentration of ferritin in the cells. The number of transferrin receptors is increased if cellular iron is low and decreased if cellular iron is high. Ferritin synthesis by the placenta may prevent excessive iron transfer to the fetus.⁹ These two mechanisms help maintain a constant flow of iron from the mother to the fetus and reduce the risk of fetal iron deficiency or toxicity. However, as will be discussed, fetal iron stores probably do reflect maternal iron status to some extent. When fetal iron demand is high, such as for the increased hemoglobin synthesis by the fetus in diabetic pregnancy, the fetus may be able to mobilize its own iron stores to support erythropoiesis.¹⁰

Iron Requirements During Pregnancy

For adult nonpregnant, menstruating women, median iron requirements are approximately 1.36 mg per day.¹¹ About half of this iron is required to replace menstrual losses. During the first trimester of pregnancy, iron requirements are lower owing to the cessation of menses, and iron stores may even increase.¹² At around 16 weeks of gestation maternal blood volume and red cell mass expand so that iron requirements increase substantially. The need for iron increases almost linearly until term. Although red cell mass expansion ceases in the last 5–10 weeks of pregnancy, in the third trimester infant erythropoiesis increases and the placenta accumulates iron. The total amount of iron required for an average pregnancy is about 840 mg.^{13,14} Of this, 350 mg is transferred to the fetus and placenta, 250 mg is lost in blood at delivery, and 240 mg is basal losses. In addition, 450 mg is used for the expansion of maternal red blood cell mass and contributes to depletion of iron stores during gestation. However, most of this iron is retained at parturition and is returned to maternal stores postpartum.¹⁵ It is important to recognize that even in industrialized countries many women enter pregnancy with no, or diminished, iron stores.^{16,17}

On average, about 5.6 mg of absorbed iron per day (range 3.5–8.8 mg per day) is needed during the second and third trimesters, or about 4.2 mg per day more than in the nonpregnant state.¹⁸ Assuming that nonheme iron intake is 12 mg per day in industrialized countries^{11,14,18} and heme iron intake is about 2–3 mg per day, of which 23% is absorbed, the average absorption of nonheme iron needs to increase

to close to 50% in the last two trimesters of pregnancy.

The actual change in efficiency of absorption in each trimester is controversial, largely because of methodologic differences among studies, including the dose of iron, whether or not the iron was given with food, the bioavailability of iron given with food, and the method used to determine absorption. For example, in unsupplemented Swedish women, absorption of a single 100 mg test dose of nonheme iron given after an overnight fast averaged 6.5% (range 1.2–11.0) at 12 weeks of gestation, 9.2% (3.2–17.9) at 24 weeks, and 14.3% (5.9–4.7) at 35 weeks.¹⁵ Absorption was estimated from whole-body counting 10–20 days after a radioactive isotope of iron was administered. Thus, the efficiency of absorption reported in this study falls far short of what is needed to provide the iron required for pregnancy, such that there would be an iron deficit of about 600 mg over the last two trimesters.¹⁸

Most studies of iron absorption during pregnancy have suffered from the limitation that iron isotopes were given in the absence of food.^{19,20} Recently, the absorption of a stable iron isotope added to food was studied sequentially in 12 unsupplemented British women.²¹ Absorption was measured by the simultaneous administration of oral and intravenous isotopes, a method that may be more valid in pregnancy than the usual approach of measuring the incorporation of an oral isotope into red blood cells.²² The meals contained 3.2 mg nonheme iron of intermediate bioavailability equilibrated with the isotope. Absorption averaged 7.2% (4.9–10.9) at 12 weeks, 36.3% (27.6–47.3) at 24 weeks, 66.1% (57.1–76.2) at 36 weeks, and 11.3% (6.0–21.2) after menses had resumed and lactation had ceased (at 16–24 weeks after delivery). Women with lower serum ferritin absorbed more iron at 12 and 24 weeks, but not at 36 weeks, when ferritin concentrations were low in all subjects. Not all became anemic. Thus, the women in this study achieved the efficiency of absorption estimated to meet their iron requirements (i.e., about 50% over the last two trimesters), yet were generally depleted of iron at the end of pregnancy.

One other serial study of iron absorption in pregnancy, conducted in Sweden, also found an approximately 10-fold rise in absorption, but values were only 1.5% at 12 weeks and 14.6% in late pregnancy.¹⁵ Possible explanations for these much lower absorption efficiencies include a lower bioavailability of iron from the meal and the fact that a large (100 mg) dose of iron was given. On the latter point, based on incorporation of an oral radioisotope of iron into red

blood cells in the third trimester, Hahn et al. showed that a 120 mg dose of iron was 9% absorbed, compared with 26% absorption of an 18 mg dose.¹⁹ Because there is at least a fivefold discrepancy among studies in the estimated amount of iron absorbed during pregnancy, further data are clearly needed on this question. Future studies should measure the absorption of iron from meals by pregnant women from populations with a low bioavailability of dietary iron and a high prevalence of iron deficiency.

Maternal hemoglobin and iron stores tend to recover spontaneously to approach prepregnancy values during the first few months postpartum,^{2,15} primarily with iron released from the breakdown of the maternal red cell mass that increased during pregnancy. The absence of menses in the early postpartum period also helps the recovery of iron stores, and the secretion of iron in breast milk is relatively low (<0.3 mg/day). Iron absorption postpartum may be somewhat elevated, especially in anemic women, but this has not been systematically evaluated against prepregnancy values. If women are supplemented with iron during pregnancy, at 2 months postpartum their iron stores may be higher than before they conceived.¹⁵ In women who become iron-depleted during pregnancy, however, full recovery of stores does not occur in the first few postpartum months.^{2,23}

Diagnosis of Iron Deficiency in Pregnancy

The most commonly used indices of iron status in pregnancy are hemoglobin and serum ferritin. Because of hemodilution during the second trimester, cutoff values (g/L) for anemia for pregnant women in trimesters 1, 2, and 3, respectively, are: hemoglobin, 110, 105, and 110; and hematocrit, 33, 32, and 33.²⁴ Even in iron-supplemented women, hemoglobin concentration falls by an average of 20 g/L in the second trimester to a mean of 116 g/L.^{2,15} The World Health Organization cutoff is 110 g/L throughout pregnancy²⁵ and 120 g/L for nonpregnant women.

In iron deficiency anemia, low hemoglobin is accompanied by additional biochemical evidence of depletion, such as low serum ferritin or transferrin saturation, or elevated erythrocyte protoporphyrin. It is difficult to make a definitive diagnosis of iron deficiency in pregnancy.⁵ Serum iron is low because of placental transfer, and transferrin increases because of normal hormonal changes, with a subsequent decrease in transferrin saturation. Mean corpuscular volume increases by 5% in pregnancy even in supplemented women, and is of little diagnostic value.² Ferritin concentrations decrease substantially during the second and third trimester owing to hemodilution and increased iron utilization, but the usual

adult cutoff for ferritin (<10 µg/L) is not corrected for pregnancy. Nevertheless, pregnant women with low serum ferritin—< 8 µg/L, a value that even occurs in about 50% of women in the United States in the third trimester—also have lower serum iron, transferrin saturation, hemoglobin, and mean corpuscular volume.⁵ In general, low serum ferritin early in pregnancy predicts lower hemoglobin in late pregnancy and deficient values for serum ferritin in both the second and third trimesters.^{2,12} A normal serum ferritin value in the first trimester does not necessarily guarantee adequate iron status in the second or third trimester.

Transferrin receptors (TfRs) are a relatively new measure of iron deficiency, and their concentration in serum increases during iron deficiency (or when there is a greater need for hematopoiesis). One study in the United States reported that 63 of 81 women with low ferritin values in the third trimester had normal serum TfR concentrations.⁵ However, almost all of the women with elevated TfR values (>8.5 mg/L) also had low levels of serum ferritin. In addition, TfR concentrations did not fall during gestation, so that in the third trimester they were the same as those of nonpregnant women. In one report they were elevated earlier in pregnancy when the major expansion of red cell mass occurs,²⁶ but no other measures of iron status were made in that study. TfRs best distinguished pregnant Jamaican women given an iron supplement from those who were not.²⁷ The receptor concentration increased by an average of 3.27 ± 0.73 mg/L in the unsupplemented group compared with a slight decline of about 0.3–0.5 mg/L in iron-supplemented women. Unlike ferritin and other iron status indicators, TfRs are unaffected by infection or inflammation²⁸ and should therefore be especially useful in countries where the prevalence of infection is high.²⁹ A combination of TfR, serum ferritin, and hemoglobin concentrations may prove to be the best indicator of iron status in pregnancy,³⁰ and perhaps infancy where the ratio of TfRs to ferritin is the same as in adults.³¹ This ratio is thought to be very sensitive to iron status because ferritin assesses the amount of storage iron whereas TfR concentrations reflect tissue iron need.³⁰

Consequences of Iron Deficiency in Pregnancy

Maternal anemia and/or iron deficiency can be harmful to both the mother and the infant. Most of the adverse effects that have been reported are poorly understood and require further documentation and quantification. Owing to the very high prevalence of iron deficiency and anemia in pregnancy, this area warrants further research.

Maternal Weight Gain

Pregnancy weight gain was positively related to maternal hemoglobin in a recent well-controlled, nonintervention study in the United States.³² However, any causality needs to be confirmed by iron intervention studies, because low iron intake is usually associated with a lower consumption of energy and other nutrients.

Maternal Mortality

Perinatal maternal mortality may be substantially higher in anemic women, especially if their anemia is severe (hemoglobin <40 g/L).^{1,33-37} This needs to be confirmed by well-designed prospective intervention studies, because most of the available data are reported associations between maternal hemoglobin and later mortality where small numbers of women who died had anemia. There has been inadequate control for potential confounding factors in nonintervention studies. For example, to some extent the higher mortality may be caused by the poorer nutritional and health status, health care, and environment of women with severe anemia. However, even moderate anemia (hemoglobin <89 g/L) was associated with twice the risk of maternal death in Britain in 1958.³⁸ The mechanisms associated with the higher mortality of anemic women are not well understood. Cardiac failure during labor has been identified as one cause in severe anemia.³ Anemic mothers may be less able to tolerate hemorrhagic blood loss during childbirth and have a greater risk of infections and slow wound healing.¹ The relative importance of these problems needs more systematic study to minimize the risk of mortality for the many women who are anemic in late pregnancy.

Maternal Morbidity

There are virtually no data on the impact of maternal anemia or iron deficiency on rates and severity of infections during pregnancy, even though iron deficiency can impair immune function. Pregnant Indian women who were severely anemic, or who had low serum iron or transferrin saturation, had lower lymphocyte stimulation indices.³⁹ In another group of pregnant Indian women, iron supplementation improved lymphocyte stimulation.⁴⁰ Future studies should record the impact of providing iron supplements during pregnancy on maternal morbidity and mortality.

Low Birth Weight and Prematurity

As early as 9–11 weeks of gestation, the time of peak chorionic gonadotropin (hCG) production, maternal hemoglobin is negatively correlated with both hCG and placental lactogen concentration

across the normal hemoglobin range.⁴¹ The placentas of anemic women are heavier, as a response to hypoxia.⁴² The placental villous tree is reduced, but the villous membrane is thinner to help maintain diffusing capacity.⁴³ By 18 weeks of pregnancy, placental volume is negatively correlated with maternal hemoglobin and serum ferritin.⁴⁴ It remains to be determined whether these early hormonal changes affect placental volume and weight.

Low birth weight is associated with both low and high maternal hemoglobin or hematocrit levels,⁴⁵ but the hemoglobin extremes could be caused by other risk factors that are actually causing the low birth weight, i.e., general malnutrition or failure of red blood cell mass to increase in the former and lack of plasma volume expansion in the latter. However, neither of these explanations has been tested empirically. In addition, because hemoglobin and hematocrit values tend to increase during the last trimester of pregnancy from a nadir in the second, lower birth weight caused by preterm delivery will usually be associated with lower hemoglobin or hematocrit.¹⁴ Iron supplements had no effect on birth weight in a well-controlled study in Finland,⁴⁶ in an English study of supplementation with vitamins and minerals including iron,⁴⁷ or in a poor Australian population.⁴⁸ In contrast, in the few studies that included substantial numbers of iron-deficient women, iron supplementation did increase birth weight significantly.⁴⁹⁻⁵¹

For many years there has been descriptive evidence of a U-shaped association between maternal hemoglobin concentration or hematocrit and shorter length of gestation.⁵²⁻⁵⁴ In a recent study that controlled for many confounding factors during data analysis, anemia was associated with a 2.7-fold increase in the relative risk of preterm delivery (< 37 weeks) and a 3.1-fold increase in low birth weight in a young, predominantly black, low-income group in the United States.³² Although this evidence for harmful effects of iron deficiency anemia is quite persuasive, several questions remain about the results of that study,⁵⁵ including why anemia without iron deficiency was not a risk factor. If confirmed, this could have major implications for who should receive iron treatment. Clearly, a prospective iron supplementation study is needed to resolve these issues, but it would be ethically difficult to include a group of anemic women who are given a placebo, especially in situations where iron supplements are provided routinely in pregnancy. In one study where 2912 women were routinely, or nonroutinely (i.e., only if a woman became anemic in two consecutive visits and until the anemia was resolved), prescribed 100 mg iron per day, the mean length of gestation

was slightly but significantly increased by 0.2 weeks by routine supplementation in boys.⁴⁶

The mechanisms by which iron deficiency or iron deficiency anemia could induce preterm delivery have not been studied.

Infant Health

Survey data collected in the U.S. Collaborative Perinatal Project⁴⁴ and in Wales⁵⁶ demonstrated a U-shaped relationship between the number of fetal abnormalities and deaths and maternal hemoglobin concentration even in early pregnancy. To what extent these associations are due to anemia alone rather than to confounders such as poor maternal health is uncertain. However, lower birth weight owing to prematurity would be a risk for infant morbidity, poor growth, and the early depletion of iron stores in infancy. As discussed below, it is also possible that iron stores are lower at birth in infants born to iron-depleted mothers, with subsequent risk of behavioral and other functional deficits.

Maternal and Infant Behavior

There are no published data on the behavioral characteristics of the offspring of anemic women. However, in different parts of the world iron deficiency anemia in infants and toddlers is associated with comparatively poor performance on developmental scales,⁵⁷ which is improved by iron supplementation.⁵⁸ Iron in the brain is involved in the synthesis of neurotransmitters that affect human behavior.⁵⁹ Iron deficiency reduces platelet monamine oxidase and the functional activity of D2 dopamine receptors.⁶⁰ It has been hypothesized from animal data that these alterations in the dopamine system mediate the observed relationships between iron deficiency anemia and cognitive derangements.⁶¹

An important question is whether maternal iron deficiency causes a lowering of the availability of iron to the young infant, with subsequent adverse effects on brain biochemistry and cognition. At birth, the amount of nonheme iron in the brain is about 10% of the total amount in adults, increasing to about 50% at 10 years of age.⁶² During the postnatal brain growth spurt the brain could be more sensitive to changes in the availability of iron. In animal models, behavioral development is also affected by iron deficiency,⁶³ with reduced motor activity and changes in the sleep cycle.

Iron deficiency anemia is likely to affect the mother's level of activity, attention, and motivation, and these effects could in turn affect the frequency and duration of interaction with her infant. Generally malnourished as well as iron-deficient infants

maintain a closer proximity to their mothers.⁶⁴ In the Nutrition Collaborative Research Support Program in Egypt, Kirksey et al. found that, compared with mothers with iron deficiency anemia, normal-iron-status mothers spent twice as much time in infant care-giving.⁶⁵ However, this needs to be confirmed in an intervention trial.

Benefits of Maternal Iron Supplementation During Pregnancy

Maternal Benefits

There is little doubt that iron supplementation in pregnancy improves maternal iron status in both industrialized and poor countries.^{2,4,15,23,27,47,66-69} Increases in hemoglobin, hematocrit, mean corpuscular volume, serum ferritin, serum iron, and transferrin saturation compared with unsupplemented controls are usually apparent within 3 months, and the usual depletion of maternal iron stores is reduced² or eliminated¹⁵ when assessed by maintenance of serum ferritin^{2,4,23,24} and bone marrow iron.¹⁹

Iron supplementation during pregnancy also improves maternal iron status postpartum. For example, Milman et al.^{23,70} supplied well-nourished Danish women with either a placebo ($n=57$) or 66 mg iron per day as ferrous fumarate ($n=63$) from 4 months of pregnancy to the end of gestation, and measured iron status until 2 months postpartum. From week 27 of pregnancy to 2 months postpartum, hemoglobin concentrations were significantly higher in the supplemented group. In the placebo group, by the end of pregnancy, 92% had exhausted their iron stores, 65% had latent iron deficiency, and 18% had iron deficiency anemia. Comparable values in the supplemented group were 54%, 6%, and 0%, respectively. Maternal serum ferritin concentrations were higher between 7 months of pregnancy and 2 months postpartum. The differences between groups were most pronounced at 2 months postpartum, when serum ferritin concentrations averaged twice those of the placebo group; in the latter group ferritin fell to prepregnancy values at 1-8 weeks postpartum. A study of Finnish women also reported that supplementation increased ferritin, but not hemoglobin, concentrations postpartum.²

More direct evidence that maternal supplementation during pregnancy increases iron stores pre- and postpartum was obtained by Svanberg et al.,¹⁵ who measured changes in maternal bone marrow iron stores during this period. In late pregnancy, no unsupplemented women had "sufficient" iron stores. In contrast, 43% of the women who took a relatively high dose supplement (200 mg iron per day)

from 16 weeks of gestation had adequate stores of iron in their bone marrow at this time. At 2 months postpartum, 90% of unsupplemented women had “sparse” iron stores versus 20% in the supplemented group.

Differences in maternal iron stores as a result of pregnancy supplementation may persist to at least 6 months postpartum, although there are relatively few studies of this. In one study of Finnish women, at 6 months postpartum there were no significant differences in hemoglobin concentrations between women who were supplemented with 200 mg iron per day and those who were unsupplemented during gestation, but mean ferritin concentrations were substantially higher (approximately 100 versus 40 $\mu\text{g/L}$).² In a small sample of women in Britain ($n=21$), at 6 months postpartum those who were supplemented during pregnancy (60 mg iron per day) had a mean ferritin concentration of 25 $\mu\text{g/L}$ compared with 15 $\mu\text{g/L}$ for the placebo group.³ The fact that iron supplementation during pregnancy can improve iron stores at 6 months postpartum may be very important in countries where the interpregnancy interval is short.

Infant Benefits

It is commonly believed that the fetus manages to obtain and store normal amounts of iron even when its mother is iron deficient, in part because of the increase in placental transferrin receptors in iron-deficient women. For example, a U.S. National Academy of Sciences committee recently concluded that “so far there is little or no evidence that routine iron supplementation is of benefit ... to indices other than the replenishment of the iron stores of the mother (*not the infant*).”²⁷

Indeed, several investigators have shown no association between maternal and infant iron status, but most of them examined the relationships between iron status in late pregnancy and iron indices in cord blood in women who were not iron deficient or who were given iron late in pregnancy. For example, no associations were found between maternal and cord blood hemoglobin or ferritin concentrations in iron-supplemented Nigerian women,^{47,71} or in French women who were supplemented if their hemoglobin fell below 110 g/L at 6 mo gestation.⁷² Similarly, Rios et al. found no difference in cord blood hemoglobin or iron status measures of infants in the United States born to iron-deficient ($n=6$) mothers compared to mothers without deficiency ($n=20$),⁷³ but the sample size was very small. Okuyama et al. observed no relationship between maternal and cord blood hemoglobin, ferritin, or total iron binding capacity ($n=35$).⁷⁴ In Hong Kong, hematologic and iron sta-

tus indices of women who were nonanemic at 36 weeks of gestation were not predictive of either hemoglobin or ferritin in cord blood.⁷⁵ Iron supplementation of one group of French mothers failed to affect cord blood iron status measures, but supplementation did not start until the third trimester.^{47,76}

In contrast, where anemia is more prevalent, cord blood iron measures have been found to be closely associated with maternal concentrations. In a group of Indian women, 60% of whom had anemia, their hemoglobin concentration at delivery was a strong predictor of cord blood (infant) ferritin concentrations, but not of cord blood hemoglobin.⁷⁷ In Nigeria, mothers with low iron stores (serum ferritin $<20 \mu\text{g/L}$) at term had significantly lower cord serum ferritin (88 $\mu\text{g/L}$) than did women with adequate stores (150 $\mu\text{g/L}$).⁷¹

Studies in industrialized countries have also reported higher maternal-fetal transfer of iron subsequent to maternal supplementation. In a recent Spanish study where 157 women all received 160 mg iron per day in the second half of pregnancy, the authors concluded that “there is no doubt about some kind of influence of the maternal iron status on the fetus.”⁷⁸ Specifically, cord blood ferritin concentrations were significantly lower (80 versus 123 $\mu\text{g/L}$) only for those infants whose mothers had serum ferritin below 12 $\mu\text{g/L}$ at 32–35 weeks of pregnancy. Maternal hemoglobin and hematocrit were significantly correlated with cord blood erythrocyte count, hemoglobin, and hematocrit values, and these were significantly lower when maternal hemoglobin fell below 110 g/L at 32–35 weeks of gestation. Maternal serum iron was correlated with cord serum iron.

In the previously discussed study by Milman et al.²³ in which 63 pregnant Danish women were given 66 mg iron daily from 16 weeks of gestation, newborn infants had higher cord serum ferritin concentrations than a placebo group ($n=27$; 155 versus 118 $\mu\text{g/L}$, $p<0.02$). Iron deficiency (cord ferritin $<80 \mu\text{g/L}$) occurred in 5% of infants in the treated group and in 26% of placebo infants. Likewise, De Benaze et al. supplemented 165 French women with either a placebo or 45 mg/day of ferrous iron starting at 3–4.5 months after conception until delivery.⁶⁶ Ferritin concentrations in cord blood were doubled by supplementation compared with controls (210 versus 102 $\mu\text{g/L}$).

Differences in maternal compliance and timing of supplementation may explain some of the disagreement between reports. In general, the above studies suggest that supplementation of the mother may need to be started before about 4 months of gestation to have a major impact on infant iron stores at birth,

especially in well-nourished women.^{23,66,70}

Another problem is that cord blood or early postpartum measures of hemoglobin, hematocrit, or ferritin may be relatively insensitive indicators of in utero iron storage. Sisson and Lund found no relationship between maternal anemia (low hemoglobin) in the late third trimester and infant hemoglobin concentrations at 3–5 days postpartum ($n=66$), but reported a “distinct” difference between the blood volumes, red cell volumes, and total circulating hemoglobin mass of infants from nonanemic ($n=12$) and severely anemic ($n=13$) mothers that reflected maternal hemoglobin in late pregnancy.⁷⁹

Almost all studies of the relationship between maternal and infant iron status have ended at birth. A stronger association might occur later in infancy; after 4–6 months, postnatal destruction of fetal hemoglobin has ended, hemoglobin and ferritin measures become more stable,⁸⁰ and breast feeding or weaning puts stress on infants’ iron stores. The only three studies extended to older infants suggest that maternal iron status during pregnancy is, in fact, a strong predictor of later infant iron status. In 1933, when breast feeding was the norm and iron-fortified infant foods were unavailable, Strauss reported that the hemoglobin and red blood cell count of newborn infants was unrelated to maternal anemia, but at 1 year of age those born to anemic mothers had half the hemoglobin concentration of infants born to nonanemic women.⁸¹

One of two more recent studies was a French investigation where 165 women received either a placebo or 45 mg ferrous iron per day from 3 to 4.5 months after conception until delivery.⁶⁶ As described previously, the cord blood of supplemented mothers contained twice the ferritin concentration of the placebo group. Equally striking is that values were 238 $\mu\text{g/L}$ (supplemented group) versus 111 $\mu\text{g/L}$ in the infants at 2 months postpartum. Unfortunately, no later measures were made.

The second longer-term investigation was the prospective Valencia Infant Anaemia Cohort study,⁸² designed to examine the relationship between iron deficiency during pregnancy and the development of iron deficiency in 156 infants. Exposure was defined as being born to a mother with iron deficiency anemia (hemoglobin <110 g/L, and ferritin <12 $\mu\text{g/L}$) at delivery ($n=63$), and cases ($n=14$) were defined as infants who developed anemia or iron deficiency anemia (hemoglobin <110 g/L and ferritin <12 $\mu\text{g/L}$) during their first year of life. Infants of anemic mothers were more likely to become anemic by 12 months of age (odds ratio 6.57), even controlling for possible confounders such as socioeconomic status, feeding practices, and morbidity. These ob-

servations need to be confirmed in an intervention study.

Because breast milk has been considered to provide an adequate amount of iron until the infant is about 6 months old, there has been relatively little concern about the iron status of young infants (i.e., < 6 months old) who are predominantly or exclusively breast-fed in developing countries. Reviews of iron prevalence in developing countries reveal that little information is available about the prevalence of anemia in this group.⁸³ Some published studies reveal a surprisingly high prevalence of anemia in the first 6 months.^{84,85} Either these infants are born with lower iron stores or the earlier iron deficit is caused by higher morbidity—although the risk of infection is usually relatively low in breast-fed infants before 6 months postpartum. There is also considerable doubt about the cutoff values for hemoglobin in this age group. Given the strong promotion, for other positive reasons, of exclusive breast-feeding for infants in poor environments, it is important to further study the timing and onset of anemia in early infancy and to determine whether it is related to maternal iron deficiency.

Recommendations for Iron Supplementation During Pregnancy

Recommendations made in 1990 by the Institute of Medicine’s Committee on Nutritional Status During Pregnancy and Lactation (United States) were to provide 30 mg iron per day.¹⁴ The recommendation was to supplement all pregnant women, regardless of iron status, because of the potential benefits to maternal and fetal health and the difficulties and cost involved in diagnosing iron deficiency throughout the course of pregnancy. The rationale for the 30 mg dose includes the fact that the efficiency of absorption falls with higher doses; 30 mg per day should provide the additional 6 mg of absorbed iron per day required; higher doses can induce side effects such as diarrhea, constipation, nausea, heartburn, and upper abdominal discomfort; and as little as 38–65 mg per day for a few weeks may reduce zinc absorption in pregnancy.⁸⁶ Supplements containing 18 mg iron per day left 52% of pregnant women with empty iron stores at 30 weeks, and 72% at 38 weeks.⁸⁷ The Institute of Medicine also recommended that the supplements should be taken in trimesters 2 and 3, when the efficiency of absorption has increased and there is less risk of pregnancy-related nausea and vomiting attributed to the supplements. However, a recent international review by the World Bank found that noncompliance with iron therapy could not often be attributed to side effects.⁸⁸

A subsequent Institute of Medicine Committee on Iron Deficiency Anemia also provided guidelines for preventing and treating iron deficiency anemia in pregnant women.⁸⁹ These are more complex, and include screening for both anemia and serum ferritin prenatally and during each trimester of pregnancy. Treatment with iron is recommended only if there is evidence of anemia and/or iron deficiency. The dose of iron to be given (30 or 60–120 mg/day) depends on the extent of deficiency. Although these recommendations may be appropriate in practices where women routinely visit their physician during pregnancy, they are less likely to be effective where resources for ferritin analyses are unavailable and when medical care during pregnancy is sporadic.

The United Nations Administrative Committee on Coordination/Sub Committee on Nutrition recommends that 60 mg ferrous iron and 250 µg folate should be supplemented in regions where there is a low prevalence of iron deficiency anemia (hemoglobin <110 g/L in <20% of women in the second half of pregnancy). In areas where the prevalence of iron deficiency anemia is high, the dose should be 120 mg elemental iron and 500 µg folate.⁹⁰

Currently there is interest in the possibility that iron supplementation once a week might be as effective as daily supplementation in improving iron status.⁹¹ This is currently being studied in pregnant women, and may affect public health strategies to improve iron status during pregnancy.

Conclusion

Iron deficiency likely affects the majority of pregnant women, even in industrialized countries. In most of these women, iron status will improve within a few months postpartum. Without iron supplementation, women who enter pregnancy with their iron stores already depleted and/or who habitually consume a diet low in bioavailable iron are likely to become progressively more iron depleted with the birth of each child and to be chronically anemic and iron deficient. There is little doubt that women in the latter situation should receive routine iron supplementation during pregnancy.

The extent to which maternal iron deficiency affects maternal and neonatal health is still uncertain. This review has described the circumstantial data suggesting that maternal anemia and/or iron deficiency is associated with premature delivery and higher maternal mortality, and possibly lower pregnancy weight gain, poorer maternal immune status, and lower birth weight. However, these outcomes have not been evaluated systematically in randomized, prospective intervention trials that include a

sufficient number of iron-deficient women, controlling for possible confounding factors. Thus, there is insufficient information to assess the overall adverse impact of anemia and iron deficiency during pregnancy.

This situation of uncertainty has led to controversy among agencies concerned with iron deficiency during pregnancy. A recent National Academy of Sciences report concluded that “the fact that iron supplementation during pregnancy has been routine in the United States for decades does not provide a body of evidence that it is, overall, advantageous; the support for the practice is based on an extrapolation from an incomplete database.”⁸⁹ In 1993, the U.S. Preventive Services Task Force (USPSTF) concluded that evidence was insufficient to recommend for or against routine iron supplementation of the pregnant woman. Their position was summarized as follows:

Although observational data suggest that pregnant women with anemia (hemoglobin levels less than 100 g/L) are at increased risk of preterm birth, low birth weight, and other adverse outcomes, it is not clear from such evidence whether anemia is responsible for these outcomes and whether they can be prevented through iron supplementation. Similarly, it is unclear whether iron supplementation during pregnancy can reduce the incidence of iron deficiency in infants, a condition that has been associated with delayed psychomotor development. Although iron supplementation can improve maternal hematological indexes, controlled clinical trials have failed to demonstrate that iron supplementation or changes in hematologic indexes actually improve clinical outcomes for the mother or the newborn.⁹²

Other groups also believe strongly that iron supplementation is unnecessary for nonanemic pregnant women. This is a widely held view in Britain^{21,93} and other European countries. For example, Barrett et al. in Britain suggested recently that “prophylactic iron supplements taken during normal pregnancy have never been shown to offer any clinical benefit; on the contrary, growing evidence exists that iron supplements may be harmful.”²¹

Another significant gap in existing information is whether maternal iron status affects the function of the infant. The USPSTF found that “future studies need to address clinical outcomes that are relevant to the health of the mother, fetus and newborn. Data examining the effects of iron supplementation during pregnancy on long-term pediatric outcomes (e.g., growth, cognitive development, school performance) are currently unavailable and should

be a focus of future research.”⁹²

Because of the very high prevalence of iron deficiency during pregnancy and the circumstantial evidence of its detrimental effects on maternal and infant function, research to answer these questions is urgently needed. Presently, millions of women remain anemic and iron deficient during pregnancy even in industrialized countries, despite public health efforts such as supplementation to alleviate this condition.^{1,14,90} It is possible that efforts to improve the situation, and compliance by mothers, might be improved if adverse impacts of iron deficiency during pregnancy were better documented. Conversely, if the impacts are minimal, it may be more appropriate on a global scale to focus on severe anemia and to view pregnancy as a situation of temporary anemia and iron depletion that does not require intervention in every woman.

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