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Anemia and iron deficiency: effects on pregnancy outcome¹⁻³

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ABSTRACT This article reviews current knowledge of the effects of maternal anemia and iron deficiency on pregnancy outcome. A considerable amount of information remains to be learned about the benefits of maternal iron supplementation on the health and iron status of the mother and her child during pregnancy and postpartum. Current knowledge indicates that iron deficiency anemia in pregnancy is a risk factor for preterm delivery and subsequent low birth weight, and possibly for inferior neonatal health. Data are inadequate to determine the extent to which maternal anemia might contribute to maternal mortality. Even for women who enter pregnancy with reasonable iron stores, iron supplements improve iron status during pregnancy and for a considerable length of time postpartum, thus providing some protection against iron deficiency in the subsequent pregnancy. Mounting evidence indicates that maternal iron deficiency in pregnancy reduces fetal iron stores, perhaps well into the first year of life. This deserves further exploration because of the tendency of infants to develop iron deficiency anemia and because of the documented adverse consequences of this condition on infant development. The weight of evidence supports the advisability of routine iron supplementation during pregnancy. *Am J Clin Nutr* 2000; 71(suppl):1280S-4S.

KEY WORDS Anemia, iron deficiency, pregnancy, maternal mortality, birth weight, preterm delivery, infants

INTRODUCTION

The provision of iron supplements to pregnant women is one of the most widely practiced public health measures, yet surprisingly little is known about the benefits of supplemental iron for the mother or her offspring during fetal or postnatal life. The purpose of this article is to examine published information on the effects of anemia and iron deficiency on pregnancy outcome and to identify current gaps in the information.

A high proportion of women in both industrialized and developing countries become anemic during pregnancy. Estimates from the World Health Organization report that from 35% to 75% (56% on average) of pregnant women in developing countries, and 18% of women from industrialized countries are anemic (1). However, many of these women were already anemic at the time of conception, with an estimated prevalence of anemia of 43% in nonpregnant women in developing countries and of 12% in women in wealthier regions (1). The prevalence of iron deficiency is far greater than the prevalence of anemia and iron deficiency

(low serum ferritin and sparse or absent stainable iron in bone marrow) often develops during the later stages of pregnancy even in women who enter pregnancy with relatively adequate iron stores (2). For this reason, and because of doubts concerning the benefits of iron supplementation on pregnancy outcome, there is uncertainty about whether routine iron supplementation of pregnant women is necessary.

Regulation of iron transfer to the fetus

Transfer of iron from the mother to the fetus is supported by a substantial increase in maternal iron absorption during pregnancy and is regulated by the placenta (3, 4). Serum ferritin usually falls markedly between 12 and 25 wk of gestation, probably as a result of iron utilization for expansion of the maternal red blood cell mass. Most iron transfer to the fetus occurs after week 30 of gestation, which corresponds to the time of peak efficiency of maternal iron absorption. Serum transferrin carries iron from the maternal circulation to transferrin receptors located on the apical surface of the placental syncytiotrophoblast, holotransferrin is endocytosed, iron is released, and apotransferrin is returned to the maternal circulation. The free iron then binds to ferritin in placental cells where it is transferred to apotransferrin, which enters from the fetal side of the placenta and exits as holotransferrin into the fetal circulation. This placental iron transfer system regulates iron transport to the fetus. When maternal iron status is poor, the number of placental transferrin receptors increases so that more iron is taken up by the placenta. Excessive iron transport to the fetus may be prevented by the placental synthesis of ferritin. As discussed later in this review, evidence is accumulating that the capacity of this system may be inadequate to maintain iron transfer to the fetus when the mother is iron deficient.

Effect of anemia on maternal mortality and morbidity

The major concern about the adverse effects of anemia on pregnant women is the belief that this population is at greater risk of perinatal mortality and morbidity (5, 6). Maternal mortality in selected developing countries ranges from 27 (India) to

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194 (Pakistan) deaths per 100 000 live births (5, 7). Some data show an association between a higher risk of maternal mortality and severe anemia, although such data were predominantly retrospective observations of an association between maternal hemoglobin concentrations at, or close to, delivery and subsequent mortality. Such data do not prove that maternal anemia causes higher mortality because both the anemia and subsequent mortality could be caused by some other condition. For example, in a large Indonesian study, the maternal mortality rate for women with a hemoglobin concentration < 100 g/L was 70.0/10 000 deliveries compared with 19.7/10 000 deliveries for nonanemic women (8). However, the authors believed that the relation of maternal mortality with anemia reflected a greater extent of hemorrhage and late arrival at admission rather than the effect of a prenatal anemic condition. In another study, often cited as showing an association between maternal anemia and subsequent mortality, approximately one-third of the anemic women had megaloblastic anemia due to folic acid deficiency and two-thirds had hookworm. The cutoff for anemia was extremely low (< 65 g hemoglobin/L), and the authors stated that although anemia may have contributed to mortality, it was not the sole cause of death in many of the women (9).

Prospective, controlled intervention trials to examine the efficacy of iron supplementation for reducing maternal mortality will be difficult to conduct because large sample sizes are required and it is considered unethical to not treat anemic women. Another point to consider is that the risk of maternal mortality can be greatly affected by the quality of health care a woman receives.

Currently, no prospective studies have proven that anemia per se increases the risk of maternal mortality, and there is inadequate information on an established hemoglobin concentration below which the risk of mortality increases. Such a cutoff value has been suggested to be as high as 89 g/L, a concentration associated with twice the risk of maternal death in Britain in 1958 (10). Hemoglobin concentration cutoffs suggested by others (9, 11, 12) need to be substantiated. The increased risk of mortality would also be more plausible and predictable if the mechanisms involved were understood. It has been suggested that maternal deaths in the puerperium may be related to a poor ability to withstand the adverse effects of excessive blood loss (12), an increased risk of infection, and maternal fatigue; however, these potential causes of mortality have not been evaluated systematically.

There is also a dearth of information on the rates and severity of infection of anemic pregnant women or iron-deficient anemic pregnant women. Iron deficiency was associated with lower lymphocyte stimulation indexes (13) and iron supplementation improved lymphocyte stimulation (14) in severely anemic pregnant Indian women. Additional studies on pregnant women are needed in which appropriate measures of immune function are evaluated in response to iron supplementation.

Maternal anemia and birth weight

The relation between maternal anemia and birth weight has been reviewed more extensively elsewhere in this issue (15). In several studies, a U-shaped association was observed between maternal hemoglobin concentrations and birth weight (16). Abnormally high hemoglobin concentrations usually indicate poor plasma volume expansion, which is also a risk for low birth weight (15, 17). Lower birth weights in anemic women have been reported in several studies (18–20). In a multivariate regression analysis of data from 691 women in rural Nepal, adjusted

decrements in neonatal weight of 38, 91, 187, and 153 g were associated with hemoglobin concentrations ≥ 20 , 90–109, 70–89 and < 70 g/L, respectively. The odds for low birth weight were increased across the range of anemia, increasing with lower hemoglobin in an approximately dose-related manner (1.69, 2.75, and 3.56 for hemoglobin concentrations of 90–109, 70–89, and 110–119 g/L, respectively) (21). Trials that included large numbers of iron-deficient women showed that iron supplementation improved birth weight (19, 22).

Some investigators reported a negative association between maternal serum ferritin and birth weight and a positive association with preterm delivery (23–25). These findings probably indicate the presence of infection, which elevates serum ferritin.

Maternal iron deficiency anemia and duration of gestation

There is a substantial amount of evidence showing that maternal iron deficiency anemia early in pregnancy can result in low birth weight subsequent to preterm delivery. For example, Welsh women who were first diagnosed with anemia (hemoglobin < 104 g/L) at 13–24 wk of gestation had a 1.18–1.75-fold higher relative risk of preterm birth, low birth weight, and prenatal mortality (16). After controlling for many other variables in a large Californian study, Klebanoff et al (26) showed a doubled risk of preterm delivery with anemia during the second trimester but not during the third trimester (26). In Alabama, low hematocrit concentrations in the first half of pregnancy but higher hematocrit concentrations in the third trimester were associated with a significantly increased risk of preterm delivery (27). When numerous potentially confounding factors were taken into consideration, analysis of data from low-income, predominantly young black women in the United States showed a risk of premature delivery (< 37 wk) and subsequently of having a low-birth-weight infant that was 3 times higher in mothers with iron deficiency anemia on entry to care. There was no such increased risk for mothers who were anemic but not iron deficient at entry to care, or for those who had iron deficiency anemia in the third trimester (28). Similar relations were observed in women from rural Nepal, in whom anemia with iron deficiency in the first or second trimester was associated with a 1.87-fold higher risk of preterm birth, but anemia alone was not. (21). In an analysis of 3728 deliveries in Singapore, 571 women who were anemic at the time of delivery had a higher incidence of preterm delivery than did those who were not anemic, but no other differences in either pregnancy complications or neonatal outcomes were observed (29). Thus, the results of several studies are consistent with an association between maternal iron deficiency anemia in early pregnancy and a greater risk of preterm delivery. The apparent loss of this association in the third trimester is probably because a higher hemoglobin concentration at this time may reflect poor plasma volume expansion and an inability to discriminate between low hemoglobin caused by iron deficiency from that caused by plasma volume expansion.

Maternal anemia and infant health

An association between maternal anemia and lower infant Apgar scores was reported in some studies. In 102 Indian women in the first stage of labor, higher maternal hemoglobin concentrations were correlated with better Apgar scores and with a lower risk of birth asphyxia (30). When pregnant women were treated with iron or a placebo in Niger, Apgar scores were significantly higher in those infants whose mothers received iron (31),

A higher risk of premature birth is an additional concern related to the effect of maternal iron deficiency on infant health; preterm infants are likely to have more perinatal complications, to be growth-stunted, and to have low stores of iron and other nutrients. In the Jamaican Perinatal Mortality Survey of >10000 infants in 1986, there was an $\approx 50\%$ greater chance of mortality in the first year of life for those infants whose mothers had not been given iron supplements during pregnancy (32), although the iron status of these infants and their mothers was not assessed. Apart from this survey, there is little known concerning the effects of maternal iron status during pregnancy on the subsequent health and development of the infant.

Benefits of iron supplementation on maternal iron status

There is little doubt that iron supplementation improves maternal iron status. Even in industrialized countries, iron supplements have been reported to increase hemoglobin, serum ferritin, mean cell volume, serum iron, and transferrin saturation (33–39). These improvements are seen in late pregnancy, even in women who enter pregnancy with adequate iron status (2, 34, 35, 37). When compared with unsupplemented pregnant women, differences in iron status due to supplementation usually occur within ≈ 3 mo of the time supplementation begins (2, 35, 40). Supplementation can reduce the extent of iron depletion in the third trimester (34). However, for women who enter pregnancy with low iron stores, iron supplements often fail to prevent iron deficiency. For example, well-nourished Danish women were given either a placebo or 66 mg Fe/d as ferrous fumarate beginning week 16 of pregnancy. At term, in the placebo group, 92% of women had no bone marrow iron, 65% of women had latent iron deficiency, and 18% of women had iron deficiency anemia. Even in the group supplemented with iron, iron stores at term were exhausted in 54% of women, although only 6% of women had latent iron deficiency and no women had iron deficiency anemia (35, 40). Iron supplements also failed to replete iron stores fully in other studies (2, 34). Low compliance may explain some of this problem.

The benefits of iron supplementation on maternal iron status during pregnancy become even more apparent postpartum. This is illustrated by a Swedish study in which all pregnant women who did not take iron supplements had less than "sufficient" iron stores in late pregnancy compared with 43% of supplemented (200 mg Fe/d) women (34). Two months after iron supplementation began, these differences were even more striking: 90% of unsupplemented women but only 20% of supplemented women, still had sparse iron stores. Several intervention studies showed that iron supplementation, beginning during the second trimester of pregnancy, resulted in higher maternal hemoglobin concentrations for ≈ 2 mo postpartum and higher serum ferritin concentrations for as long as 6 mo after delivery than observed in unsupplemented control subjects. In Denmark, for example, serum ferritin concentrations at 2 mo postpartum in women supplemented during pregnancy were twice those of women who did not receive iron (35). A Finnish study showed that iron supplementation during pregnancy improved maternal serum ferritin, but not hemoglobin, concentrations for ≥ 6 mo postpartum (2). Compared with a placebo group, women in Niger who were supplemented with iron during pregnancy had higher concentrations of hemoglobin, serum iron, and serum ferritin; higher mean cell volumes; and lower erythrocyte protoporphyrin at 3 mo postpartum. At 6 mo postpartum, erythrocyte protoporphyrin was still significantly lower in the iron-supplemented group (31).

These benefits on postpartum maternal iron status may be especially important when interpregnancy intervals are short because the supplemented mother will enter a subsequent pregnancy with better iron status. In addition, many women are anemic in the postpartum period because of blood loss during delivery. Although a similar benefit could be obtained if women were supplemented during lactation, pregnancy is a time when iron absorption is particularly efficient and when there is usually more opportunity to provide, encourage, and monitor the use of supplements.

Insufficient attention has been paid to the extent to which anemia affects the mother's quality of life, including her level of fatigue and ability to cope with the stress of pregnancy and a young infant. Such outcomes should be assessed in future studies.

Benefits of maternal iron supplementation on iron status of the fetus and infant

It is generally assumed that the iron status of the fetus, and subsequently the infant, is quite independent of maternal iron status during pregnancy (40), except perhaps when infants are born to severely anemic women. A review of the literature on this issue indicates that indeed, with rare exceptions (41), there is no significant association between maternal hemoglobin concentrations at or near term and cord blood hemoglobin concentrations. This lack of an association was reported in countries as diverse as Niger (31), India (42), China (43), Japan (44), and Ireland (45). A lack of association between maternal and cord blood hemoglobin was also found in France (37) and Denmark (46), even when half of the women were provided with iron supplements. However, although there was no relation between low hemoglobin concentrations in unsupplemented British women in the third trimester and hemoglobin concentrations in infants 3–5 d postpartum, infants born to nonanemic mothers had distinctly higher blood volumes, red cell volumes, and circulating hemoglobin mass than those of infants born to anemic mothers (47).

Cord blood ferritin was, however, related to maternal hemoglobin or maternal ferritin in most of these and other nonintervention and intervention studies (37, 41, 42, 44, 46, 48, 49) with few exceptions (45, 50, 51). In the study by Rusia et al (51), serum transferrin receptor concentrations were higher in infants born to anemic mothers. De Benaze et al (37) found the relation between the iron status of French pregnant women and serum ferritin concentrations of their infants to still be apparent 2 mo postpartum (37). Similarly in Turkey, maternal hemoglobin at delivery was correlated with serum ferritin in 2-mo-old infants (52). Colomer et al (53) analyzed the relation between the hemoglobin concentration of pregnant women and the risk of anemia in their infants at 12 mo of age. Infants born to anemic mothers were more likely to become anemic themselves (odds ratio: 5.7), when feeding practices, morbidity, and socioeconomic status were controlled for (53). Because of the high prevalence of iron deficiency in infants after ≈ 6 mo of age, especially in developing countries, there is a clear need for more studies that assess the relation between the iron status of pregnant women and the iron status of their infants postpartum, preferably in controlled interventions. Any association will be more difficult to detect when infants are fed iron-fortified foods from an early age. Preterm delivery associated with iron deficiency could also contribute to lower fetal iron stores. Nonetheless, the effect of the mother's iron status on her infant's iron stores postpartum needs to be clarified because of the known detrimental effects of iron deficiency anemia on the mental and motor development of infants.

CONCLUSIONS

This review showed many gaps in our knowledge about the adverse effects of maternal anemia and iron deficiency on pregnancy outcome. Such disparities include inadequate documentation of anemia's effects on maternal mortality, morbidity, and well-being, and on infant health and development. Likewise, the benefits of maternal iron supplementation on these outcomes are unclear, even for women who develop anemia during pregnancy. However, there is substantial evidence that maternal iron deficiency anemia increases the risk of preterm delivery and subsequent low birth weight, and accumulating information suggests an association between maternal iron status in pregnancy and the iron status of infants postpartum. Certainly, iron supplements improve the iron status of the mother during pregnancy and during the postpartum period, even in women who enter pregnancy with reasonable iron stores. The advisability of routine iron supplementation during pregnancy, regardless of whether the mother is anemic, has been heavily debated in the United States (40, 54), and routine supplementation is not universally practiced in all industrialized countries (55). In my opinion, the mass of evidence supports the practice of routine iron supplementation during pregnancy, although iron supplementation is certainly most important for those pregnant women who develop anemia. ☐

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