Maternal iron status: relation to fetal growth, length of gestation, and iron endowment of the neonate

Theresa O Scholl

Anemia prevalence is highest in preschool children, women of reproductive age, and women who are pregnant. While the etiology of anemia is multifactorial, iron deficiency is the most commonly recognized nutritional cause. Observational studies imply that supplementation with iron or iron-folic acid should be started early in pregnancy, if not before, in order to prevent low-birth-weight and preterm delivery. Despite this, findings from clinical trials, even those conducted during early pregnancy, are equivocal. Recent follow-up studies of children born to women supplemented with iron-folic acid suggest that mortality is decreased and that the infant’s iron endowment reflects the mother’s iron status during pregnancy.

INTRODUCTION

Anemia, as measured by low hemoglobin or hematocrit, affects nearly one-quarter of the world’s population. Worldwide, its prevalence is highest in preschool children (47.4%), women of reproductive age (30.2%), and women who are pregnant (41.8%). Among pregnant women, the prevalence of anemia in Africa exceeds 50%, while it exceeds 40% in Asia and exceeds 30% in Latin America and Oceania. Anemia is generally less frequent among pregnant women in Europe (18.7%) and North America (6%), except for in low-income and minority populations in the United States; in this group, prevalence is high, reaching 7.6%, 12.1%, and 33.8% for trimesters 1, 2, and 3, respectively. The etiology of anemia is multifactorial and includes hemoglobinopathies, acute infections, chronic inflammation, and diets poor in nutrients such as folate, B12, and vitamin A, along with iron, which is the most commonly recognized nutritional cause.

PREVALENCE AND ETIOLOGY OF IRON DEFICIENCY

Iron deficiency is defined by three stages of increasing severity: depletion of iron stores (stage 1), iron deficiency without anemia (ID) (stage 2), and iron deficiency anemia (IDA) (stage 3). Changes in erythropoiesis are a late manifestation of ID evidenced by an abnormally low concentration of hemoglobin or hematocrit. As with anemia, the risk of ID is elevated during early childhood, in women of reproductive age, as well as during pregnancy. ID is associated with an inadequate intake of absorbable iron in the face of a circumstance that increases the need for extra iron, e.g., rapid growth during the first 2 years of life, loss of iron in menstrual blood in women, and the increase in red cell mass and growth of the fetus during pregnancy.

Many women of childbearing age have a dietary intake of absorbable iron that is too low to offset losses from menstruation and the increased requirement associated with gestation. Data from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994) show a median dietary intake of 14.7 mg/day of iron for pregnant women, suggesting that approximately 90% were below the estimated average requirement for pregnancy (22 mg/day). Recent participants from the Camden Study (2001–2007 [unpublished data]) had a similar iron intake from food (15 mg/day at the median), with 83% below the estimated average requirement for pregnancy (Table 1).
Dietary intakes of iron and other micronutrients are associated with ID during pregnancy. While energy-adjusted intakes of protein and carbohydrate were similar among groups in the Camden Study, pregnant women with 3rd trimester ID, based upon two abnormal tests (ferritin < 12 ng/mL and transferrin saturation < 15%), had diets that were significantly lower (based on an average of three 24-h recalls) in iron, B12, B6, riboflavin, and folate \((P = 0.07)\) and higher in fat than gravidae who were not iron deficient (Table 2). In addition to a poor-quality diet, other important causes of ID in women include poor iron absorption and blood loss from menstruation, through labor and delivery, or from rapid repeat pregnancy.4–6

During pregnancy, the maternal body requirement for iron increases to approximately 1,000 mg, on average.4,6 This amount covers 350 mg associated with fetal and placental growth, 500 mg associated with expansion in red cell mass, and 250 mg associated with blood loss at delivery. The increased requirement needs to be supported by higher maternal iron intakes, increasing from 6 mg/day in the 1st trimester, to 19 mg/day in the 2nd trimester, to 22 mg/day in the 3rd trimester of pregnancy.4,6 In order to meet these increased requirements, gravidae must draw upon iron stores, consequently increasing the risk of ID and IDA. Among non-pregnant women aged 16–49 years from NHANES III, the prevalence of IDA, estimated from low hemoglobin and two of three additional laboratory tests for ID, was 2–5%, while ID occurred in 11–16%.7,8 A body iron model that utilized soluble transferrin receptors and serum ferritin gave a lower prevalence for ID, amounting to 9.2% in women of reproductive age between the ages of 20 and 49 years.8 Among gravidae in the Camden Study (2001–2007), there was a substantial rise in maternal anemia between trimesters 1 and 3. Likewise, ID (based upon low serum ferritin of <12 ng/mL and transferrin saturation of <15%), rose by trimester from 5%, to 14.4%, to 40%, and IDA (defined using CDC criteria for anemia by trimester with ID)6 increased from 0.9%, to 3%, to 17% during trimesters 1, 2, and 3, respectively (Figure 1). Predictive values would, of course, be higher in developing countries where IDA is more prevalent. While supplementation with iron or iron-folic acid is beneficial for improving maternal hemoglobin levels during pregnancy and reducing the risk of maternal anemia, daily supplementation may increase the risk of a maternal hemoglobin count that exceeds 130 g/L, but the clinical significance of this is uncertain.9

### Table 1

**Usual intakes of iron from food (mg/day) by pregnant women in the NHANES III (1988–1994) and Camden (2001–2007)**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>NHANES III</th>
<th>Camden Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>24 mg/day</td>
<td>28 mg/day</td>
</tr>
<tr>
<td>90</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>75%</td>
<td>17.6</td>
<td>19</td>
</tr>
<tr>
<td>50% (median)</td>
<td>14.7</td>
<td>15</td>
</tr>
<tr>
<td>25%</td>
<td>12.2</td>
<td>12</td>
</tr>
<tr>
<td>10%</td>
<td>10.2</td>
<td>9</td>
</tr>
<tr>
<td>5%</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>SEM</td>
<td>0.75</td>
<td>0.23</td>
</tr>
<tr>
<td>N</td>
<td>346</td>
<td>997</td>
</tr>
<tr>
<td>% below EAR</td>
<td>90%</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Abbreviations: EAR, estimated average requirement; SEM, standard error of the mean.

*Unpublished data.

### Table 2

**Summary of energy-adjusted nutrient intakes from food that are associated with 3rd trimester iron deficiency, as observed in the Camden Study (2001–2007 [unpublished data]).**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Iron deficient*</th>
<th>Not iron deficient*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/day)</td>
<td>88 ± 1.5</td>
<td>88 ± 1.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Carbohydrate (g/day)</td>
<td>286 ± 4.8</td>
<td>294 ± 4</td>
<td>0.15</td>
</tr>
<tr>
<td>Fat (g/day)</td>
<td>87 ± 1.6</td>
<td>83 ± 1.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Iron (mg/day)</td>
<td>15.5 ± 0.5</td>
<td>16.9 ± 0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Folate (mcg/day)</td>
<td>307 ± 12.7</td>
<td>337 ± 10.5</td>
<td>0.07</td>
</tr>
<tr>
<td>B12 (mcg/day)</td>
<td>4.0 ± 0.4</td>
<td>5.1 ± 0.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Vitamin A (IU/day)</td>
<td>5072 ± 3.51</td>
<td>5530 ± 287</td>
<td>0.30</td>
</tr>
<tr>
<td>B6 (mg/day)</td>
<td>1.9 ± 0.05</td>
<td>2.0 ± 0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Riboflavin (mg/day)</td>
<td>2.0 ± 0.04</td>
<td>2.2 ± 0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Zinc (mg/day)</td>
<td>12.1 ± 0.32</td>
<td>12.5 ± 0.26</td>
<td>0.41</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>917 ± 25</td>
<td>967 ± 21</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Mean of three 24-h recalls (performed at entry and at 20 and 28 weeks gestation) adjusted for age, parity, ethnicity, smoking, body mass index, and energy intake.

† Iron deficiency based upon two abnormal tests: serum ferritin (<12 mg/mL) and transferrin saturation (<15%) at week 28.
The best time to detect risk associated with maternal anemia may be early in pregnancy, before the plasma volume is fully expanded. While maternal red cell mass and maternal plasma volume both increase during gestation, they do not do so simultaneously. Hemoglobin and hematocrit decline throughout the 1st and 2nd trimesters, reach their lowest point late in the second to early in the 3rd trimester, and then rise again near term, with peak hemodilution occurring at 24–26 weeks. Anemia utilizes CDC definition. Iron deficiency anemia is anemia with iron deficiency.

PREGNANCY OUTCOME AND MATERNAL ANEMIA

The best time to detect risk associated with maternal anemia may be early in pregnancy, before the plasma volume is fully expanded. While maternal red cell mass and maternal plasma volume both increase during gestation, they do not do so simultaneously. Hemoglobin and hematocrit decline throughout the 1st and 2nd trimesters, reach their lowest point late in the second to early in the 3rd trimester, and then rise again near term, with peak hemodilution occurring at 24–26 weeks. As a result, physiologic anemia from normal expansion of the maternal plasma volume is difficult to distinguish from true anemia, particularly late in pregnancy.

This was originally examined in the Camden Study by separating anemia by time (early versus later in gestation) and etiology (IDA and anemia from other causes). Early in pregnancy, there were clear differences in mean corpuscular volume and diet in women with IDA that were absent during the 3rd trimester. Early IDA was associated with greater than twofold increases in the risks of a low-birth-weight or preterm delivery, while anemia from other causes was associated with a decreased risk of preterm birth. The association of IDA in early pregnancy or early maternal anemia with preterm delivery and other poor outcomes was consistent with data from the Collaborative Perinatal Project in the United States and studies from England, Wales, and the developing world, including China, Nepal, and Egypt.

High maternal hemoglobin has consistently been associated with failure of the plasma volume to expand and with adverse outcomes related to maternal pathology, such as maternal hypertension, preeclampsia, or diabetes. Recent studies have raised the possibility that giving too much iron to nonanemic women, i.e., daily administration of 50–60 mg/day, can increase hemococoncentration and the poor outcomes associated with it. Increased levels of the iron storage protein ferritin are also associated with preterm delivery, but this likely occurs via infection and inflammation. Thus, both extremes of the maternal hemoglobin distribution are associated with adverse pregnancy outcomes, with low hemoglobin reflecting a mix of true and physiologic anemia and high hemoglobin reflecting failure of the plasma volume to expand. Poorly nourished animals have reduced maternal plasma volume expansion during pregnancy, and low cardiac output, lower uteroplacental blood flow, and reduced nutrient transmission to the fetus. It is possible that hypovolemia, along with anemia, has nutritional antecedents.

RANDOMIZED TRIALS WITH IRON OR IRON-FOLIC ACID IN PREGNANT WOMEN

Observational data on anemia imply that supplementation should be started early in pregnancy, if not before, in order to prevent low birth weight and preterm delivery. There have been two such trials in the United States and several others in China, Nepal, Mexico, and Australia. In both of the US studies, low-income and minority nonanemic women were enrolled before 20 weeks’ gestation; the women were then randomly assigned to receive supplemental iron or placebo or to receive multivitamins with or without iron. In one trial, the proportion of women with absent iron stores and IDA at week 28 was improved by the supplemental iron, while in the other
there was little change. In both studies, supplemented gravidae had significantly longer gestations and higher infant birth weights with a reduced risk of delivering low-birth-weight or preterm low-birth-weight infants.

In Nepal, a comparison of four micronutrient regimens showed that an iron-folic acid supplement with vitamin A significantly decreased low-birth-weight deliveries (by 19%) and small-for-gestation births (by nearly 10%) compared to vitamin A alone. In a second Nepalese trial, a comparison of multiple micronutrients with the iron-folic acid control showed increased infant birth weight (+77 g) and decreased risk of low birth weight (45%) for the group receiving micronutrients. Neither study showed an effect of the supplements on risk of preterm delivery or gestation duration.

In China, gravidae from Hong Kong with hemoglobin levels between 80 and 140 g/L at baseline (<16 weeks) were randomly assigned to receive either 60 mg supplemental iron or placebo to determine if iron increased risk of gestational diabetes. While gestational diabetes risk was not altered with supplemental iron, birth weight was increased significantly (+96 g), and risk of small-for-gestational age (SGA) births was significantly reduced (3.6% versus 7.5%), with gestation duration (38.8 versus 38.7 weeks) and preterm delivery (6.4% versus 6.7%) remaining unchanged. A second trial took place in a rural area of northwestern China, with villages randomly assigned to folic acid (control), iron-folic acid, or multiple micronutrients at week 14 gestation, on average. Supplementation with iron-folic acid increased gestation duration (+0.23 weeks) and reduced risk of very preterm delivery (<34 weeks (0.98% versus 1.8%) compared to supplementation with folic acid alone. Infant birth weight was increased significantly with multiple micronutrients (+42 g) but not with iron-folic acid (+20 g). Both Chinese trials thus showed higher hemoglobin levels and improvements in birth weight or gestation duration among supplemented women. However, a randomized trial of non-anemic Australian gravidae who were supplemented before gestational week 20, showed no improvement in birth weight or gestation among iron-supplemented pregnant women.

Anemia in early pregnancy and IDA are associated with increased risk of adverse outcomes of pregnancy, but clinical trials, even those conducted during early pregnancy are equivocal. A recent Cochrane review found that women receiving iron folic acid supplements gave birth to infants that were significantly heavier (+58 g) than women receiving placebo or other regimens, but there was no difference in the incidence of preterm delivery, SGA, or low birth weight. The authors opined that pooling results may not be the best way to evaluate studies that are not only statistically heterogeneous but also vary in the dose and/or duration of iron or iron-folic acid supplementation as well as in the maternal subjects’ backgrounds. A poor maternal diet that results in anemia is unlikely to occur in isolation, even in developed countries, and the effects may not be correctable by a brief period of supplementation. In the developing world, hookworm and malaria infestation compound the effects on maternal anemia of chronic undernutrition, early childbearing, and short intervals between pregnancies. Supplementation with iron or iron-folic acid may need to be started before pregnancy and continued throughout the reproductive years, in order to prevent low-birth-weight and preterm deliveries.

**IRON OR IRON-FOLIC ACID SUPPLEMENTATION AND INFANT MORTALITY**

Since preterm delivery, fetal growth restriction, and low birth weight are known causes of infant mortality, supplementation with iron, or iron-folic acid, if beneficial, might also be expected to increase infant survivorship. Offspring born to iron-folic acid-supplemented mothers from rural China and to those supplemented with multiple micronutrients had lower neonatal mortality compared to offspring of controls receiving folic acid alone. The difference was significant only for the iron-folic acid group, for whom there was a 54% decrease in neonatal mortality associated with fewer deaths from complications of preterm birth (6.8% versus 15%) and birth asphyxia (4.1% versus 11%). In Niger, while women supplemented with iron from later gestation (week 28) onward did not show differences in either the birth weight of offspring or the duration of gestation, there were fewer fetal/neonatal deaths (1% versus 7%) among the offspring of iron-supplemented mothers. In Nepal, despite the association of higher birth weights with multiple micronutrient supplementation, fewer early neonatal deaths (23.4/1,000 versus 9.1/1,000) and perinatal deaths (49.0/1,000 versus 40.5/1,000) occurred among the offspring of the iron-supplemented controls. A post-hoc comparison of the two Nepalese trials suggested that neonatal and perinatal mortality were significantly lower among offspring of women supplemented with iron-folic acid compared with those who received micronutrients. Long-term follow-up of Nepalese children showed a significant 31% decrease in mortality between birth and age 7 years for children born to mothers whose diets were supplemented with iron-folic acid while pregnant.

**IRON STORES IN PRETERM AND SMALL-FOR-GESTATION INFANTS**

The higher rates of preterm delivery and low (or lower) birth weight associated with anemia and IDA likely con-
tribute to poor neonatal iron stores. From week 32 of gestation until delivery, fetal iron stores increase as the fetal liver grows. Most (>66%) of the infant’s total body iron is acquired during the final trimester of pregnancy. An early preterm birth deprives the infant of the opportunity to acquire iron. Total body iron, hemoglobin, and ferritin are all lower in preterm infants. Between 25% and 85% of preterm infants develop ID during their first postpartum year and the condition develops earlier than in term infants. An infant weighing 1,500 g has half the body iron content of an infant with a birth weight of 3,000 g. A term infant of low birth weight is also likely to have a smaller liver size and poorer iron stores than an infant whose birth weight is appropriate. SGA infants born to women with hypertension or preeclampsia also have decreased iron stores due to poor placental function with decreased iron transport. A study of 84 low-birth-weight Chilean infants who were preterm (either appropriate for gestational age [AGA] or SGA) or term SGA showed that the term SGA infants had higher cord hemoglobin levels than preterm AGA infants who, in turn, had higher levels of ferritin than infants who were both preterm and SGA. After birth, the limited iron stores of preterm infants are unable to support postnatal erythropoiesis and catch-up growth. Preterm infants, both AGA and SGA, had lower hemoglobin concentrations by 4 months of age compared to term SGA infants.

MATERNAL IRON STORES AND INFANT IRON ENDOWMENT

Another influence on infant iron stores, apart from lower birth weight and shorter gestation duration, is maternal ID. Studies on rhesus macaques suggest that the iron status of the infant after birth reflects that of the mother before pregnancy. Serum ferritin levels, but not hemoglobin or hematocrit, were lower in infants born to iron-deficient macaques and the levels correlated with the mother’s pregravid transferrin saturation. In humans, mothers with low levels of ferritin had cord blood ferritin levels that were 30–60% below those of women with better iron stores. Data reviewed by Allen suggest that ferritin in cord blood usually correlates with maternal ferritin or hemoglobin measured at delivery; however, there appears to be little relationship between maternal hemoglobin and cord blood hemoglobin, except in the case of severe anemia. Mild maternal anemia is associated with increased serum erythropoietin in the mother and in the cord. Chronic fetal hypoxia from reduced uteroplacental blood flow increases hemoglobin production in the fetus via increased erythropoietin and has been documented to occur in SGA infants. Greater erythropoietin production may be the underlying reason for similar levels of hemoglobin in the cords of infants born to anemic and non-anemic women, i.e., the erythropoietin enhances oxygen delivery and promotes the growth of fetal organs and tissues in a hypoxic environment.

Infants born at term with an appropriate weight for gestation have iron stores that are adequate for approximately 6 months, while those born preterm or who are SGA have smaller stores. As the rate of postnatal growth increases, infant hematological status declines. In macaques, the infant’s mean corpuscular volume was significantly lower across the first 6 months if the mother was iron deficient before pregnancy. In humans, one common assumption has been that the iron status of offspring is independent of maternal iron status during pregnancy. In a study performed by Colomer et al., 156 infants were followed during their first year; risk of developing anemia was increased 6.57-fold for those infants whose mothers had anemia, as defined by low hemoglobin with low ferritin (<12 ng/mL) at delivery. A stratified analysis suggested that risk was independent of infant birth weight, feeding practice, and other variables.

Term infants born to anemic and non-anemic Jordanian mothers were followed from delivery to age 12 months. While there were no differences in cord blood levels for any hematologic variables, by 9 months of age, the infants of anemic women had lower hemoglobin and red cell indices; the cumulative incidence of IDA, as defined by low hemoglobin and low ferritin or high zinc protoporphyrin, was 81% in the infants of anemic mothers and 65% in infants born to controls. Infants of anemic Javanese mothers, who weighed more than 2,500 g at birth, had approximately a twofold increased risk of low hemoglobin (<100 g/L) at 3–5 months (adjusted odds ratio [AOR] 1.81, 95% CI 1.34–2.43) compared to non-low-birth-weight infants of non-anemic mothers; those weighing <2,500 grams were at higher risk of anemia (AOR 3.7, 95% CI 1.69–8.02). However, risk was not greatly increased (AOR 1.15, 95% CI 0.61–2.16) for low-birth-weight infants of mothers without anemia. As might be expected, the smaller iron stores associated with low birth weight interact with anemia in the mother to increase the offspring’s anemia risk by nearly fourfold. Thus, follow-up studies of infants born to anemic women suggest that the infant’s iron endowment mirrors that of the mother. Additional research is required to confirm or deny whether increased erythropoietin production is associated with maternal anemia and has given rise to the notion that the iron endowment of offspring is unrelated to that of the mother during pregnancy.

CONCLUSION

Iron supplementation during pregnancy increases maternal iron status and stores; it is, therefore, plausible that
iron supplementation improves pregnancy outcome when the mother is anemic or from a population in which anemia prevalence is high. A poor maternal diet resulting in anemia is unlikely to occur in isolation and its effects may not be correctable by a brief period of supplementation. Supplementation with either iron or iron–folic acid may need to be started before pregnancy and continued throughout the reproductive years in order to reduce the risk of adverse pregnancy outcomes and to improve the iron stores of offspring. Since preterm delivery, fetal growth restriction, and low birth weight are known causes of infant mortality, supplementation with iron, or iron–folic acid, might also increase infant survivorship, as recent research is beginning to suggest.

Follow-up studies of infants born to anemic women also indicate that the infant’s iron endowment mirrors that of the mother despite the fact that many investigators find similar levels of hemoglobin in infants born to anemic and non-anemic women. Increased erythropoietin production, an adaptation that enhances oxygen delivery and promotes growth of fetal organs and tissues in the hypoxic environment, may be responsible, but more research in this area is needed.

At the other extreme, high maternal hemoglobin and high levels of the iron storage protein ferritin have consistently been associated with an increased risk of adverse outcomes. It is possible that giving too much iron to nonanemic women, i.e., daily administration of 50–60 mg/day, can increase hemoconcentration and the risk of poor outcomes like preeclampsia or gestational diabetes.

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**REFERENCES**


