The Potential Impact of Iron Supplementation during Adolescence on Iron Status in Pregnancy\textsuperscript{1,2}

Sean R. Lynch

Eastern Virginia Medical School, Medical Service, Hampton Veterans Affairs Medical Center, Hampton, VA 23667

ABSTRACT Iron deficiency anemia (IDA) during pregnancy is associated with significant morbidity for mothers and infants. Over 50\% of pregnant women in developing countries suffer from IDA. It is also prevalent among adolescent girls because the growth spurt and onset of menstruation increase iron requirements. Women who conceive during or shortly after adolescence are likely to enter pregnancy with low or absent iron stores or IDA. Iron supplementation during adolescence is one of the new strategies advocated to improve iron balance in pregnancy. However, iron requirements are highest in the second and third trimesters and the model described here indicates that iron balance at this stage depends more on adequate intakes of bioavailable iron than on the size of the iron stores at conception. Furthermore, although supplementation will correct anemia and increase iron stores in girls, the positive effect on iron status will be temporary if their diets do not contain adequate bioavailable iron. Although iron status in early pregnancy may be improved if the period of supplementation continues up to the time of conception, supplementation before pregnancy should be viewed as an additional strategy to supplementation during the second and third trimesters. J. Nutr. 130: 448S–451S, 2000.

KEY WORDS: • iron supplementation • adolescence • pregnancy

Iron deficiency anemia reduces physical work capacity and the ability to earn income (Dallman 1982, Levin 1986). Verbal learning, memory and physical performance may also be impaired in iron-deficient adolescent girls (Bruner et al. 1996, Nelson 1996). If these young women become pregnant, they are exposed to additional risks. Iron deficiency anemia during pregnancy is associated with premature delivery, low birth weight and increased perinatal mortality (Bothwell et al. 1979, Godfrey et al. 1991, Scholl et al. 1992). Infants born to iron-deficient mothers also have a higher prevalence of anemia in the first 6 mo of life (Preziosi et al. 1997). Maternal mortality is increased in women whose hemoglobin levels fall to below 6–7 g/dL (Bothwell et al. 1979).

The consequences of iron deficiency anemia outlined above are cogent reasons for supporting programs designed to reduce its prevalence in pregnancy. Routine iron supplementation is recommended in the second and third trimesters because most women cannot meet their increased iron requirements from dietary sources alone (Bothwell et al. 1979). However, although efficacious in carefully conducted clinical trials, its effectiveness when implemented on a national scale has been disappointing (Yip 1994). Putative reasons for the discrepancy between efficacy and effectiveness include the cost and logistics of supplying iron tablets, the inadequacy of delivery systems at the primary care level, insufficient counseling about the potential benefits and side effects of iron supplements, and poor compliance among pregnant women. Programmatic alternatives for delivering iron supplements are therefore being sought.

It has been suggested that adolescence may be an optimal time in which to deliver iron supplements to build iron stores before pregnancy. Physiologic needs are high at this stage of life because of increased requirements for the expansion of the blood volume associated with the adolescent growth spurt and the onset of menstruation (Dallman 1992). It is also a time when supervised iron supplementation may be possible, e.g., in school-based programs. However, because iron absorption is closely regulated in the body and because the body limits the size of iron stores, it is questionable whether supplementation during adolescence can in fact build sufficient stores before pregnancy to substitute for the need for supplementation during pregnancy. This analysis is an attempt to predict the potential benefit of such programs for iron balance in subsequent pregnancies. It is based on an examination of the physiologic factors controlling iron balance before and during pregnancy.

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iron requirements in pregnancy

Physiologic iron requirements are three times higher in pregnancy than they are in menstruating women. Approximately 1200 mg must be acquired from the body iron store or from the diet by the end of pregnancy to meet both the requirements of the mother for the expansion of her circulating red cell mass and the demands of the developing fetus. The average requirement for a menstruating woman for the same period of time is ~400 mg. The increased requirement is therefore ~800 mg.

The demand for additional iron is not spread evenly throughout pregnancy. In the first trimester, requirements are actually reduced because menstruation has ceased, the demands of the fetus are still small and the expansion of the maternal red cell mass has not yet started to occur. The need for additional iron commences early in the second trimester and reaches a peak toward the end of the third trimester, when requirements rise to between 4 and 6 mg/d.

Sources of the additional iron required during pregnancy

The relative importance of iron stores on the one hand and increased iron absorption on the other is best illustrated by examining iron balance during pregnancy in women from industrialized countries. They enter pregnancy with adequate stores. The additional iron is derived from both the stores and increased absorption. The serum ferritin level is the best measure of the size of iron stores; 1 μg/L serum ferritin = 8 mg storage iron in an adult (Bothwell et al. 1979). The 50th percentile for serum ferritin concentrations reported in the National Health and Nutrition Examination Survey (NHANES) III for women in the United States aged between 20 and 44 y is 36 μg/L (Looker et al. 1991). This value predicts a mean iron store of ~300 mg. Therefore the average size of iron stores for women entering pregnancy in the United States is ~300 mg. Because the estimated total additional requirement during pregnancy calculated above is 800 mg, the average woman must absorb 500 mg (~2 mg/d) more iron than she required while menstruating to avoid a negative iron balance.

However iron absorption is regulated by the size of body iron stores (Finch 1994). The operation of this important regulatory process is not affected by the advent of pregnancy. Women who enter pregnancy with adequate iron stores absorb relatively little iron during the first trimester. Stores are utilized first as the demand for iron increases in the second trimester. Absorption is accelerated only after there has been a substantial fall in the size of the iron store (Bothwell et al. 1979, Hallberg and Hulten 1996). At the time of the greatest need in late pregnancy, stores are essentially exhausted in most women. Virtually all of the iron is derived from absorption.

A study carried out by Barrett et al. (1994) in a group of women living in the United Kingdom demonstrates the relationship between iron stores and nonheme iron absorption in pregnancy. These women consumed a bioavailable diet that supplied about 12 mg nonheme iron/d. Absorption of the heme iron in the diet was not measured. They received no iron supplements. The relevant observations drawn from the study are summarized in Table 1.

The results show that the women utilized iron stores first. Absorption increased markedly only after most of the storage iron had been used. At the time of highest iron requirement in the third trimester, virtually all of the iron was derived from absorption. The women were able to reach the end of pregnancy without becoming anemic because they entered pregnancy with adequate iron stores and their diets contained a sufficient quantity of highly bioavailable iron to allow absorption to be increased approximately ninefold. The diets of women in developing countries do not contain sufficient bioavailable iron to meet these needs during the second and third trimesters even if iron stores are adequate at the beginning of pregnancy. Supplementation will be necessary in the second and third trimesters of pregnancy even if supplementation before conception improves iron storage status in the first trimester.

Potential benefits of iron supplementation during adolescence

Iron supplementation during adolescence is expected to have significant benefits unrelated to pregnancy, including a reduction in the prevalence of anemia, improved physical performance and better cognitive function. It may also have benefits for pregnancy. A reduction in the burden of anemia for adolescents entering pregnancy would be anticipated. Furthermore, some studies suggest that an adequate iron supply during the first trimester may have a beneficial effect on infant birth weight (Scholl et al. 1992). However it is important to note that the benefit of iron supplementation in terms of

<table>
<thead>
<tr>
<th>Supplement dose (mg)</th>
<th>Average daily iron intake (mg)</th>
<th>Initial absorption (mg %)</th>
<th>Final absorption (mg %)</th>
<th>Initial ferritin (μg/L)</th>
<th>Final ferritin (μg/L)</th>
<th>Final iron store (mg)</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>12.0</td>
<td>2.0 (16.7)</td>
<td>2.0 (16.7)</td>
<td>10</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>60/wk</td>
<td>20.6</td>
<td>3.4 (16.7)</td>
<td>2.0 (9.7)</td>
<td>10</td>
<td>17.2</td>
<td>138</td>
</tr>
<tr>
<td>120/wk</td>
<td>29.0</td>
<td>4.8 (16.7)</td>
<td>2.0 (6.9)</td>
<td>10</td>
<td>24.2</td>
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<td>30/d</td>
<td>42.0</td>
<td>7.0 (16.7)</td>
<td>2.0 (4.7)</td>
<td>10</td>
<td>35.5</td>
<td>279</td>
</tr>
<tr>
<td>60/d</td>
<td>72.0</td>
<td>12.0 (16.7)</td>
<td>2.0 (2.8)</td>
<td>10</td>
<td>60.0</td>
<td>480</td>
</tr>
</tbody>
</table>

1 Data from Barrett et al. (1994).

2 Calculated (1 μg/L serum ferritin = 8 mg storage iron).

TABLE 1

Iron stores in women entering pregnancy in the United States is calculus for women entering pregnancy in the United States aged between 20 and 44 y.

TABLE 2

Predicted effect of iron supplementation (different doses for ~12 wk) on stores and the percentage of iron absorption.
accumulating iron stores is temporary, especially for women whose menstrual losses are in the upper-normal range. When supplementation is initiated in an iron-deficient individual, the percentage of absorption is high. More iron is absorbed than is needed to replace losses. The additional iron is used to correct any anemia or functional tissue iron deficiency present. Iron not needed by the functional compartment enters the store. As stores increase, absorption is down-regulated. A new equilibrium is eventually established, and then the quantity of iron absorbed (derived from both the diet and the supplement) again matches the requirement. The percentage of absorption is now much lower than it was before supplementation. When the supplement is withdrawn, the percentage of absorption from the diet will initially be equal to that at the end of the period of supplementation. Because the quantity of iron now being ingested is much less, a period of negative iron balance will ensue. Storage iron will be consumed to make up the difference between requirements and absorption. The store will gradually diminish with a concomitant rise in the percentage of absorption until the presupplementation balanced state is again reached. The predicted changes in iron storage size and the percentage of iron absorption can be calculated from the well-established relationship between the size of iron stores and the percentage of iron absorption (Cook 1990, Hulten et al. 1995).

Table 2 shows the predicted changes in absorption and the size of the iron store in teenage women with relatively high menstrual losses (70th percentile for healthy Western teenagers, Hallberg and Rossander-Hulten 1991) who are given various supplements. This example was chosen because women with high menstrual losses are at greatest risk for iron deficiency.

The predicted increase in iron stores ranges from 58 mg (138 – 80) for women receiving a weekly supplement of 60 mg to 400 (480 – 80) in those receiving a daily 60-mg supplement. Iron stores will be accumulated initially at a rate ranging between 1.4 mg/d for the 60 mg/wk supplement (absorption 3.4 mg/d, excretion 2 mg/d) and 10 mg/d for the 60 mg/d supplement (absorption 12 mg/d, excretion 2 mg/d). The rate falls exponentially as the stores increase, eventually returning to the balanced state with a daily absorption equivalent to the daily loss (2 mg in this example). The average rate of storage iron accumulation over the whole period of adaptation to the higher iron intake will therefore equal one half of the initial rate, ranging from 0.7 mg/d for the 60 mg/wk supplement to 5 mg/d for the 60 mg/d supplement. In all cases, the new steady state will be reached in about 80 d. The illustration is for an individual with a normal hemoglobin level. Anemic women will take a longer period of time to reach the new steady state because of the iron requirement for correcting the anemia.

If the supplement is withdrawn, the percentage of iron absorption from the diet will be too low initially to maintain iron balance because the store regulator has been set for the higher iron intake during the period of supplementation. Iron will be withdrawn initially from the store to make up the shortfall. The initial rate of loss from stores will equal the difference between the requirement and the rate of absorption at the time the supplement is withdrawn. As the stores are used up, the rate of absorption will increase proportionately until it again matches requirements. The average rate of consumption of storage iron will therefore equal half the initial rate. The period of time between removal of the supplement and reestablishment of the presupplementation steady state is expected to be between 5 and 16 mo (Table 3). It is important to note, however, that iron will be derived initially primarily from the store. Absorption will rise in an exponential fashion in concert with reduction in iron storage size. As a consequence, half of the iron store will be lost over a period considerably less than half the time required to return to the original steady state. The amount of storage iron available for pregnancy will therefore be relatively small if the supplement is discontinued several months before conception.

The results of a recent study by Angeles-Agdeppa et al. (1997) provide some support for the validity of the model presented. They reported the serum ferritin levels in adolescent women given various supplemental regimens for 12 wk. The highest values (63.4 μg/L) were achieved by the women given 60 mg/d. In all cases, serum ferritin levels were again close to the baseline levels 6 mo after the supplements had been discontinued. It is therefore evident that the improvement in storage iron status in early pregnancy that can be achieved by supplementation during adolescence is modest if more than a few months separate the end of the supplementation period from the time of conception.

LITERATURE CITED
