Recommendation Statement

Screening for Iron Deficiency Anemia--Including Iron Supplementation for Children and Pregnant Women

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force (USPSTF) is redesigning its recommendation statement in response to feedback from primary care clinicians. The USPSTF plans to release, later in 2006, a new, updated recommendation statement that is easier to read and incorporates advances in USPSTF methodology. This recommendation statement is an interim version that combines existing language and elements with a new format. Although the definitions of grades remain the same, other elements have been revised.

Summary of Screening Recommendations

Screening Children and Pregnant Women for Iron Deficiency Anemia

- The U.S. Preventive Services Task Force (USPSTF) concludes that evidence is insufficient to recommend for or against routine screening for iron deficiency anemia in asymptomatic children aged 6 to 12 months. **Rating: I recommendation**

- The USPSTF recommends routine screening for iron deficiency anemia in asymptomatic pregnant women. **Rating: B recommendation**

Rationale

Importance: Iron deficiency anemia is associated with psychomotor and cognitive abnormalities in children. Iron deficiency anemia during pregnancy has been associated with increased risk of low birth weight, preterm delivery, and perinatal mortality. The prevalence of iron-deficiency anemia has remained stable over the last decade in the general U.S. population and continues to be highest among minority and poor children. Recent studies suggest that maternal iron deficiency anemia may be associated with postpartum depression and poor performance on mental and psychomotor tests in offspring.

Detection: There is good evidence that hemoglobin is a sensitive test for iron deficiency anemia, but it has low specificity because the majority of anemias in childhood are not caused by iron deficiency. The USPSTF found insufficient evidence (no studies) that specifically addressed the accuracy of screening tests in asymptomatic pregnant women.

Benefits of detection and early intervention: The USPSTF found no evidence that universal or selective screening for iron deficiency anemia in asymptomatic children results in improved health outcomes. The USPSTF found poor evidence (conflicting studies) of the effectiveness of interventions that demonstrate improved health outcomes, such as developmental status, in asymptomatic children. The USPSTF found fair evidence that treating asymptomatic pregnant women who have iron deficiency anemia results in moderate benefits in health outcomes.

Harms of detection and early treatment: The USPSTF found no evidence addressing the harms of screening either children or pregnant women for iron deficiency anemia. Potential harms include false-positive results, anxiety, and cost; the small potential harms of treatment with oral iron include gastrointestinal symptoms and unintentional overdose.

USPSTF assessment: The USPSTF was unable to determine the balance between the benefits and harms of routine screening for iron deficiency anemia in asymptomatic children aged 6 to 12 months. The USPSTF concludes that the benefits of routine screening for iron deficiency anemia in asymptomatic pregnant women outweigh the potential harms.

Summary of Supplementation Recommendations

Iron Supplementation for Children and Pregnant Women

- The U.S. Preventive Services Task Force (USPSTF) recommends routine iron supplementation for asymptomatic children aged 6 to 12 months who are at increased risk for iron deficiency anemia (see Clinical Considerations for a discussion of increased risk). **Rating: B recommendation**

- The USPSTF concludes that evidence is insufficient to recommend for or against routine iron supplementation for asymptomatic children aged 6 to 12 months who are at average risk for iron deficiency anemia. **Rating: I recommendation**

- The USPSTF concludes that evidence is insufficient to recommend for or against routine iron supplementation for non-anemic pregnant women. **Rating: I recommendation**

Rationale

Importance: Iron deficiency anemia is associated with psychomotor and cognitive abnormalities in children. Iron deficiency anemia in pregnancy has been associated with increased risk of low birth weight, preterm delivery, and perinatal mortality. Recent studies suggest that maternal iron deficiency anemia may be associated with postpartum depression and poor performance on mental and psychomotor tests in offspring. The prevalence of iron-deficiency anemia has remained stable over the last decade in the general U.S. population and continues to be greatest among minority and poor children.

Recognition of risk status: A validated risk assessment tool to guide primary care physicians in identifying individuals who would benefit from iron supplementation has not been developed.

Benefits of risk assessment and preventive medication: The USPSTF found fair evidence that iron supplementation (e.g., iron–fortified formula or iron supplements) may improve neurodevelopmental outcomes in children at increased risk for iron deficiency anemia. The USPSTF found poor evidence (poor quality and conflicting studies) that iron–fortified formula or supplementation improves neurodevelopmental outcomes in children aged 6 to12 months if they are not at increased risk for iron deficiency anemia. The USPSTF found poor evidence (poor quality studies) that iron supplementation may improve health outcomes in non-anemic pregnant women.

Harms of risk assessment and preventive medication: The USPSTF found fair evidence that oral iron supplementation increases the risk for unintentional overdose and gastrointestinal symptoms. Given appropriate protection against overdose, these harms are small. There is poor evidence (poor quality studies) that iron supplementation for non-anemic pregnant women results an increased risk for harms

USPSTF Assessment: The USPSTF concludes that the moderate benefits of iron supplementation in asymptomatic children aged 6 to 12 months who are at increased risk for iron deficiency anemia outweigh the potential harms. The USPSTF was unable to determine the balance between the benefits and harms of iron supplementation in children aged 6 to 12 months who are at average risk for iron deficiency anemia, and of iron supplementation in non-anemic pregnant women.

Clinical Considerations

- These USPSTF recommendations address screening for iron deficiency anemia and iron supplementation in children aged 6 to 12 months who are at increased risk and average risk, in asymptomatic pregnant women, and in non-anemic pregnant women. Infants younger than 6 months of age, older children, non-pregnant women, and men are not addressed.

- Iron deficiency anemia can be defined as iron deficiency (abnormal values for serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin) with a low hemoglobin or hematocrit value. Iron deficiency is much more common than iron deficiency anemia and is part of a continuum that ranges from iron depletion to iron deficiency anemia. Many of the negative health outcomes of iron deficiency are associated with its extreme manifestation, iron deficiency anemia. Iron deficiency has also been associated with negative neurodevelopmental outcomes in children.

- Other causes of anemia vary by population and include other nutritional deficiencies, abnormal hemoglobin (e.g., thalassemia), enzyme defects, and anemia associated with acute and chronic infections.

- In the U.S., race, income, education, and other socioeconomic factors are associated with iron deficiency and iron deficiency anemia. Individuals considered to be at high risk for iron deficiency include adult females, recent immigrants and, among adolescent females, fad dieters, and those who are obese. Premature and low birth weight infants are also at increased risk for iron deficiency.

- Venous hemoglobin is more accurate than capillary hemoglobin for identifying anemia. Ferritin has the highest sensitivity and specificity for diagnosing iron deficiency in anemic patients.

- Iron deficiency anemia is usually treated with oral iron preparations. The likelihood that iron deficiency anemia identified by screening will respond to treatment is unclear because many families do not adhere to treatment and because the rate of spontaneous resolution is high. 97% of infant formula sold in the U.S. is iron-fortified. Substantial reductions in the incidence of iron deficiency and iron deficiency anemia have been demonstrated in healthy infants fed iron-fortified formula or iron-fortified cereal, compared with infants fed cow's milk or unfortified formula.

- Iron supplements accounted for 30% of fatal pediatric pharmaceutical overdoses occurring between 1983 and 1990, and iron poisoning has been observed even in the context of controlled trials in which parents were instructed in the safe storage and use of iron products. A reduction in deaths of children due to iron overdose was observed when unit-dose packaging was required between 1998 and 2002; this requirement was overturned by the courts in 2003.

Discussion

Burden of Illness

Iron deficiency anemia is uncommon in the United States. Overall, the prevalence of iron deficiency anemia has remained stable over the past decade at 7% in children aged 1 to 2 years; 9% in adolescent females; and 2%-5% in non-pregnant females. More detailed data on the prevalence of iron deficiency anemia in infants of different ages has not been identified. The prevalence among pregnant women is uncertain. (1)

Iron deficiency, the most common nutritional deficiency in the world, can be caused by a number of factors. In infants, such factors are rapid growth, inadequate dietary intake, blood loss, decreased absorption, and prematurity. In women of childbearing age, such factors are heavy menstrual blood loss and pregnancy. (1)

In children, iron deficiency anemia has been associated with psychomotor and cognitive abnormalities, poor school performance, and mental retardation. Longitudinal studies indicate that anemic children diagnosed in infancy continue to be developmentally delayed after 10 years of follow-up. It is difficult to establish a causal relationship between anemia and developmental abnormalities in longitudinal studies due to environmental, socioeconomic, and other nutritional confounding factors. Iron deficiency anemia in pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality, as well as decreased parental interaction and poorer developmental outcomes in infants. Reduced work productivity, endurance, and exercise capacity have been associated with anemia in adults. Adults with severe anemia are at risk for cardiopulmonary complications. (1)

Scope

The USPSTF examined new evidence addressing:

1) The overarching question of whether screening for iron deficiency anemia results in improved neurodevelopmental outcomes.
2) The effectiveness of interventions since the publication of its 1996 recommendation, Screening for Iron Deficiency Anemia-Including Iron Prophylaxis in Children and Pregnancy. (2)

The Task Force also examined the literature addressing other evidence linking screening (e.g., prevalence, the accuracy of screening tests, and harms of screening and interventions) to improved health outcomes.

Accuracy of Tests

Serum hemoglobin or hematocrit is the primary screening test for identifying anemia. Hemoglobin is sensitive for iron deficiency anemia; however, it is not sensitive for iron deficiency because mild deficiency states may not affect hemoglobin levels. Hemoglobin is also nonspecific, since many cases of anemia are due to causes other than iron deficiency. The positive predictive value of low hemoglobin for iron deficiency in children 12 months of age has been shown to range from 10% to 40%. (1) In infants, particularly before 12 months of age, iron deficiency and iron deficiency anemia often resolve spontaneously, reducing the positive predictive value of any screening test. The sensitivity and specificity of using other single tests (e.g., serum ferritin, transferrin saturation, and erythrocyte protoporphyrin) as primary screening tools for iron deficiency anemia have not been well studied. There was insufficient evidence (no studies) to specifically address the accuracy of screening tests in asymptomatic pregnant women.

Children

Intervention--Treatment

The USPSTF found poor evidence (conflicting studies) that treatment of iron deficiency anemia results in improved neurodevelopmental outcomes. In a randomized control trial in an Indonesian clinic, 12- to 18-month-old infants treated for iron deficiency anemia demonstrated a significant improvement in Bayley developmental scores compared with a control group at 4 months of follow-up.(3) A Cochrane review, published in 2001 found 7 trials of treatment in children up to 3 years of age; the review concluded that there was a lack of clear evidence that treatment of iron deficiency anemia has a beneficial effect on psychomotor development. (4)

Intervention--Supplementation

Previous randomized and nonrandomized controlled trials, observational studies, and time series studies have demonstrated a substantial decrease in the incidence of iron deficiency and iron deficiency anemia in healthy infants as a result of iron supplementation (e.g., iron-fortified formula, iron-fortified cereal) compared with infants fed cow's milk or unfortified formula. Three randomized controlled trials published since the 1996 USPSTF review measure motor, cognitive, or behavioral outcomes in average-risk infants (2 fair-quality studies) and infants at increased risk for iron deficiency anemia (1 fair-quality study). (1)

In assessing iron supplementation in average risk infants, the USPSTF found poor evidence (conflicting studies) that supplementation results in improved outcomes. In a fair quality randomized controlled trial average risk infants who received oral iron supplementation had increased Bayley psychomotor scores at 13 months compared with the control group (100 ± 12 vs. 93 ± 9; normal range 85 to 115); Bayley mental developmental scores did not differ between the groups. (5) Another fair-quality RCT conducted in average risk infants found no differences in Bayley mental and psychomotor scores at 18 months. (6) The USPSTF found fair evidence that iron supplementation (e.g., iron–fortified formula or iron supplements) provides moderate benefits in children at increased risk. In a fair quality randomized control trial conducted in England, a smaller decrease in Griffith's global developmental quotient at 24 months of age was demonstrated in infants at increased risk for iron deficiency anemia who were fed iron-fortified formula compared with the control group of infants who received unmodified cows' milk. (7)

Harms of Screening and Treatment

The USPSTF found no new evidence regarding the potential harms of screening for iron deficiency anemia in infants and children. Potential harms of screening include false-positive results, anxiety, and cost. Unintentional overdose is a known potential harm of treatment with oral iron, as are gastrointestinal symptoms. Given appropriate protection against overdose, these harms are small. Cohort studies have reported no important adverse effects with iron-fortified formula, nor were serious side effects reported in the clinical trials of iron fortified food or formula.

Pregnant Women

Intervention--Treatment

The USPSTF found poor evidence (poor quality studies) that treatment of asymptomatic pregnant women with iron deficiency anemia improves health outcomes for the mother. While most studies of treatment found no effect on birth outcomes, a recent but flawed RCT found a substantial increase in the birthweight of infants whose mothers received treatment. (1)

Intervention--Supplementation

There is good evidence that iron supplements improve the hematological indices of pregnant women. However, the USPSTF found poor evidence (poor quality studies) that iron supplementation in non-anemic pregnant women improves health outcomes for mother or neonate. A Cochrane review found that iron supplementation prevents low hemoglobin at birth or at 6 weeks post-partum in the neonate, but concluded there were no reliable data from controlled trials about the pregnancy outcomes for either mother or baby. (8)

Harms of Screening and Treatment

The USPSTF found no evidence on the harms of screening for iron deficiency anemia in asymptomatic pregnant women. Potential harms are the same as those found in children. There is poor evidence (poor quality studies) on the potential harms of iron supplementation in non-anemic pregnant women. Unintentional overdose of young children in the home is a known potential harm of supplementation with oral iron. Another potential harm of iron supplementation is higher Caesarean section rates. In one Finnish trial of pregnant women, routine iron supplementation led to higher rates of Cesarean sections and post partum blood transfusions. Study investigators attributed the increased cesarean sections and blood transfusion rates to possible anxiety by midwives and obstetricians about low hematocrit values in the selectively supplemented group. (9)

Research Needs

Iron deficiency anemia in infancy is a marker for subsequent poor neurocognitive development; however, screening and early treatment have not consistently improved neurocognitive outcomes. It is possible that prevention of neurodevelopmental consequences of iron deficiency anemia may require the prevention of iron deficiency rather than the detection and treatment of existing iron deficiency. Another possibility is that the prevention of neurodevelopmental consequences may require screening and early treatment of multiple nutritional deficiencies, rather than iron deficiency anemia alone. At present there is little evidence to support these hypotheses, but additional studies, particularly in developing countries, may confirm them. (1)

Recommendations of Others

The Centers for Disease Control and Prevention (CDC) recommends screening for iron deficiency anemia in high-risk infants, high-risk preschool children, pregnant women, and non-pregnant women of childbearing age. The CDC also recommends universal iron supplementation to meet the iron requirements of pregnancy.(10)

The American Academy of Pediatricians (AAP) recommends screening for all infants between the ages of 9 to 12 months and then 6 months later; for children at high risk, screen once a year from ages 2 to 5 years. The 2005 AAP breastfeeding guidelines recommend continuing breastfeeding for at least the first year of life and beyond, while introducing complementary foods rich in iron beginning around 6 months of age; breastfed infants weaned before 12 months of age should receive iron-fortified infant formula. AAP recommends that preterm and low birth weight infants receive iron supplementation before 6 months of age.(11,12)

The American Academy of Family Physicians (AAFP) recommends screening for iron deficiency anemia in high-risk infants aged 6 to 12 and in infants whose principal dietary intake is unfortified cow's milk.

The American College of Obstetricians and Gynecologists (ACOG) recommends prenatal screening for all women at the earliest prenatal visit and early in the third trimester.

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APPENDIX A

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE
STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

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