Screening and Routine Supplementation for Iron Deficiency Anemia: A Systematic Review

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abstract

BACKGROUND AND OBJECTIVES: Supplementation and screening for iron-deficiency anemia (IDA) in young children may improve growth and development outcomes. The goal of this study was to review the evidence regarding the benefits and harms of screening and routine supplementation for IDA for the US Preventive Services Task Force.

METHODS: We searched Medline and Cochrane databases (1996–August 2014), as well as reference lists of relevant systematic reviews. We included trials and controlled observational studies regarding the effectiveness and harms of routine iron supplementation and screening in children ages 6 to 24 months conducted in developed countries. One author extracted data, which were checked for accuracy by a second author. Dual quality assessment was performed.

RESULTS: No studies of iron supplementation in young children reported on the diagnosis of neurodevelopmental delay. Five of 6 trials sparsely reporting various growth outcomes found no clear benefit of supplementation. After 3 to 12 months, Bayley Scales of Infant Development scores were not significantly different in 2 trials. Ten trials assessing iron supplementation in children reported inconsistent findings for hematologic measures. Evidence regarding the harms of supplementation was limited but did not indicate significant differences. No studies assessed the benefits or harms of screening or the association between improvement in impaired iron status and clinical outcomes. Studies may have been underpowered, and control factors varied and could have confounded results.

CONCLUSIONS: Although some evidence on supplementation for IDA in young children indicates improvements in hematologic values, evidence on clinical outcomes is lacking. No randomized controlled screening studies are available.

REVIEW ARTICLE

Iron-deficiency anemia (IDA), defined as iron deficiency (serum ferritin <12 μg/L) with hemoglobin levels <110 g/L,[1,2] can present a significant burden of disease in infancy and childhood. Iron is required in the production of hemoglobin, an essential protein found in red blood cells, and is stored in the body for use in hemoglobin production. Iron deficiency occurs when the level of stored iron becomes depleted. IDA occurs when iron levels are sufficiently depleted to produce anemia, characterized by hypochromic microcytic red blood cells.[3] Although infants in the United States with iron deficiency are usually asymptomatic, IDA has been associated in some observational studies with cognitive and behavioral delays in children. However, these studies had methodologic flaws[4]; for example, the outcomes examined were varied and not clearly clinically important. The effect of IDA in infancy and childhood has been reported in few well-designed, long-term controlled studies.

Iron deficiency among infants and toddlers in the United States has a prevalence of ~8% in the general population[5–7]; however, only about one-third of children who are iron deficient have associated anemia.[5,8,9] The prevalence of IDA in children between the ages of 1 and 5 years is estimated to be ~1% to 2% in the United States.[8,10] The prevalence in children from low-income families is estimated to be slightly higher (ie, ~3% for boys and 4% for girls based on 1 study of 432 one- to three-year-old children residing in California).[7] Current evidence regarding the prevalence of IDA in infants <1 year old in the United States is lacking, although estimates for low-risk infants in other developed countries range from 2% to 4%.[11,12] Screening young children for IDA may lead to earlier identification and therefore earlier treatment, which has the potential to prevent negative health outcomes. However, the advent of iron fortification in the United States in many children's food products may influence our current understanding of IDA.

In 2006, the US Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to recommend for or against routine screening for IDA or routine iron supplementation for asymptomatic children aged 6 to 12 months who are at average risk for IDA (I Recommendations).[13] These recommendations were based on a lack of evidence that screening resulted in improved health outcomes, as well as poor and conflicting evidence regarding the benefit of iron supplementation in children who are not at increased risk of IDA. At that time, the USPSTF recommended routine iron supplementation for asymptomatic children aged 6 to 12 months who are at increased risk for IDA (B Recommendation), based on evidence that iron supplementation may improve neurodevelopmental outcomes in children who are at increased risk of IDA, which outweighs any potential harms.

The present review was commissioned by the USPSTF to update the previous recommendations.[13] The scope of this review includes evidence regarding the benefits and harms of routine iron supplementation, screening for IDA in children ages 6 to 24 months, and the association between a change in iron status and improvement in child health outcomes in populations relevant to the United States.

METHODS

Detailed methods and data for this review (including search strategies, inclusion criteria, abstraction and quality rating tables, information on risk factors and risk assessment tools, and results related to biochemical and composite intermediate outcomes) are provided in the full report.[14] The protocol was developed by using a standardized process[15] with input from experts and the public. In consultation with the USPSTF, analytic frameworks and Key Questions were developed for routine supplementation (Supplemental Appendix Figure 2) and for screening for IDA (Supplemental Appendix Figure 3) to show the linkages between Key Questions and bodies of evidence.

A research librarian searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews (through the second quarter, 2014), and Medline (1996–August 2014) for relevant studies to update the previous USPSTF reviews.[16,17] Because the previous research focused on systematic reviews and key studies of treatments for IDA, we also searched the reference lists of systematic reviews[18–20] to identify any additional, relevant studies published before 1996.

Studies were selected on the basis of inclusion and exclusion criteria developed for each Key Question. Articles were selected for full review if they were related to IDA in children who received an intervention (supplementation or screening and related treatment) between the ages of 6 and 24 months. We restricted inclusion to English-language articles and excluded studies published only as abstracts. For all Key Questions, the focus was on studies that involved iron supplementation and treatment regimens commonly used in clinical practice in the United States. We excluded studies conducted in resource-poor populations, including nutritionally deficient populations in developing countries and populations in areas expected to have a high prevalence of hemoparasites, by selecting studies conducted in countries listed as having "high" or "very high" human development based on the international United Nations Human Development Index.[21] At least 2 reviewers independently evaluated each study to determine eligibility.

Clinical outcomes of study were morbidity (including growth; cognitive, psychomotor, and neurodevelopmental outcomes; and diagnosis of developmental delay), mortality, and quality of life. Harm outcomes included accidental overdose, study discontinuations, and other harms related to screening, supplementation, or treatment. Included intermediate outcomes were incidence of IDA, iron deficiency, and anemia, as well as hematologic indices such as ferritin levels. Randomized controlled trials, nonrandomized controlled clinical trials, and controlled cohort studies were included for all Key Questions.

Details about the study design, patient population, setting, screening method, interventions, analysis, follow-up, and results were abstracted. A second investigator reviewed the data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF[15] to rate the internal validity (quality) of each study as good, fair, or poor. Discrepancies were resolved through a consensus process. When otherwise not reported and where possible, relative risks (RRs) and 95% confidence intervals (CIs) or P values were calculated.

The aggregate quality of the body of evidence for each Key Question (ie, good, fair, poor) was assessed by using methods developed by the USPSTF; these assessments were based on the number, quality and size of studies; consistency of results between studies; and directness of evidence.[15] Meta-analysis was not attempted due to the limited number of studies for each Key Question and differences among studies in design, population, and outcomes.

RESULTS

Figure 1 shows the results of the literature search and selection process.

Routine Iron Supplementation

Benefits of Routine Iron Supplementation in Children Ages 6 to 24 Months

A 1996 review conducted for the USPSTF[17] found adequate evidence that iron prophylaxis resulted in reductions in the incidence of iron deficiency and IDA, but few data focusing on clinical outcomes were reported. The 2006 update[16] did not assess the effect of supplementation on intermediate outcomes, and it found mixed evidence regarding the benefit of iron supplementation on neurodevelopmental test scores.

Overall, 10 trials of iron supplementation were included in this update.[22–34] One study was rated as good quality,[29] 7 as fair quality,[22–28,32] and 2 as poor quality.[30,31] In general, children were enrolled between 6 and 9 months of age. Iron supplementation was administered for durations ranging from 3 to 18 months. Supplementation was provided as oral iron drops, iron-fortified formula, and as iron-fortified milk, foods, or meat. Controls used in the studies varied, and included a non-iron-containing formula or supplement, a specific diet, cow's milk, or nothing. Race or ethnicity was poorly reported. Enrolled sample sizes ranged from 24 to 493, except for 1 larger study of 1798 children; many studies analyzed fewer numbers due to loss to follow-up or refusal to undergo venipuncture. Only 1 study analyzed children on an intention-to-treat basis[29]; the proportion of the sample available for analysis at the end of the other studies ranged from 53% to 92%. Most studies excluded children born prematurely and those with conditions likely to affect iron absorption, growth, or development, thus ruling out some children at higher than average risk for IDA but not specifically targeting those at average risk.

Methodologic shortcomings included unclear methods of randomization and allocation concealment,[25–27,30–32] lack of or unclear methods of

blinding,[22,23,25,27,30,31] and high or differential loss to follow-up.[24,27,28,30,31] In addition, studies may be underpowered; although 7 studies reported some power or sample size calculations, they were limited to certain outcomes and varying differences in effect sizes.[24,26–29,31,32] For example, 2 studies were reported to be powered for developmental outcomes, with 1 sufficient to detect a 5-point difference on the Bayley Scales of Infant Development[28] and 1 sufficient to detect a 2.5-point difference in "developmental scores" (scale not mentioned).[26] We did not pool the results because of the heterogeneity of the studies in terms of supplementation method, dose, duration, timing of initiation and follow-up, and methodologic limitations. In addition, risk factors were largely not reported, and no studies stratified results according to risk groups.

Six fair-quality placebo-controlled trials of routine iron supplementation in young children sparsely reported various growth outcomes; 5 trials found no clear effect of supplementation on weight, length, or head circumference after 3 to 12 months of follow-up (Table 1).[22,25,26,28–30] As noted earlier, studies may have been underpowered to detect growth outcomes. Most sample sizes varied from 70 to 428, with 1 study including 1657 children. The only study reporting statistically significant differences in growth parameters found lesser growth values in the iron-supplemented group, possibly due to baseline differences in these growth outcomes.[26] The group that received iron began the study with lesser values (weight: 7.98 vs 8.09 kg; length: 66.6 vs 66.9 cm [both $P < .01$]). Although this study was the largest, it was conducted in Chile, had a high incidence of IDA in the control group (22.6%), and suffered from methodologic flaws. Children were
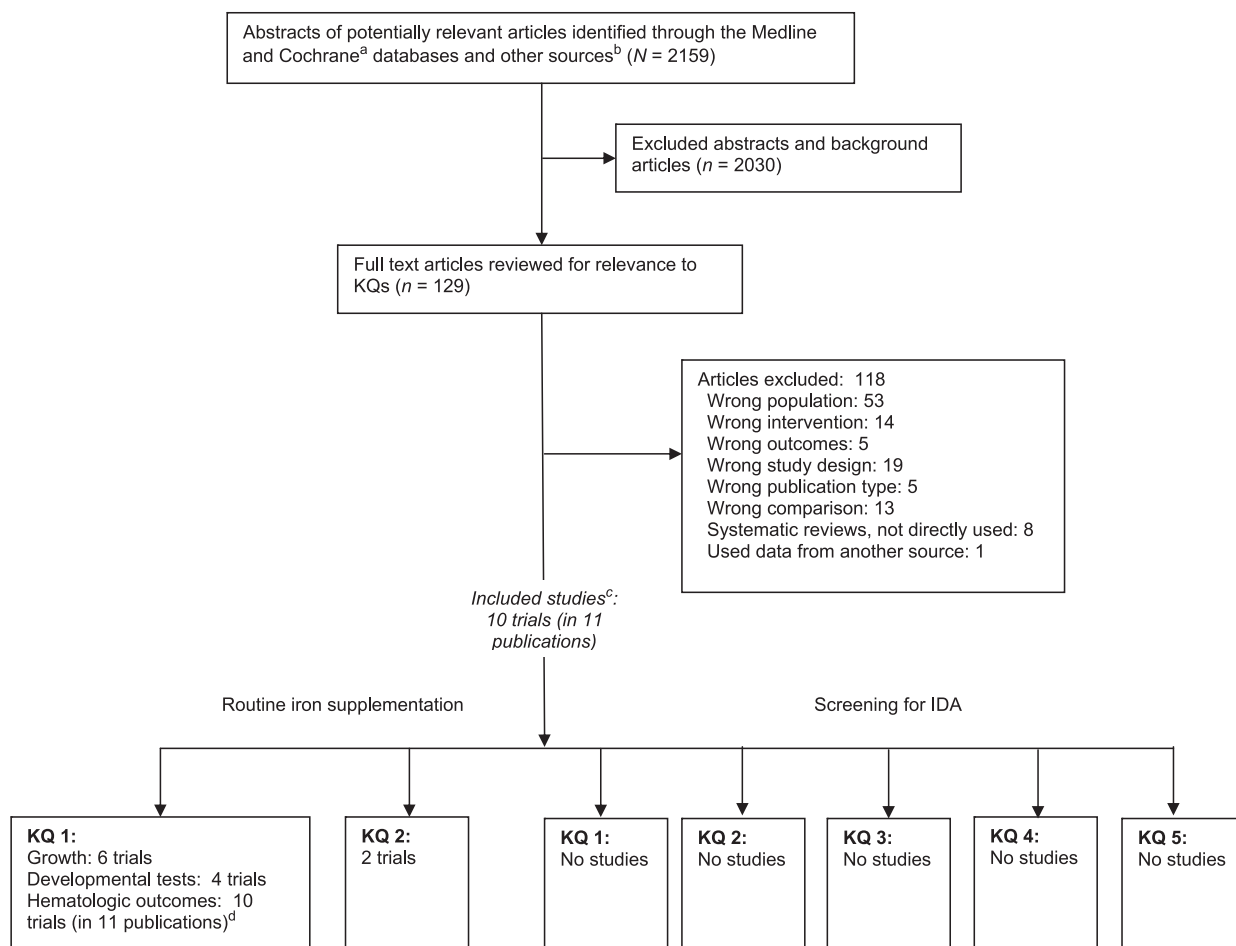
FIGURE 1

Literature flow diagram. [a]Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. [b]Other sources include previous reports, reference lists of relevant articles, and systematic reviews. [c]Some studies are included for >1 Key Question (KQ). [d]Includes 2 poor-quality studies.

initially randomized to receive low- or high-iron supplementation, but the low-iron intervention was replaced with a no-iron intervention partially through the study, partly because the interim analysis suggested that the low-iron condition was sufficient to prevent IDA. For analysis, all children who received any iron supplementation were combined and compared with children who did not receive supplementation, breaking randomization and leading to baseline differences between the groups. Because randomization was broken, we viewed the results as a fair-quality, comparative observational study. The authors found the following significant results for the iron-supplemented versus

no-iron groups, respectively, after 12 months: weight, 10.0 vs 10.1 kg ($P < .05$); length, 74.7 vs 75.1 cm ($P < .001$); length for age (z score), −0.27 vs −0.15 ($P < .01$); and head circumference, 46.7 vs 47.0 cm ($P < .001$); the changes were significant possibly because the iron-supplemented group had lower values at baseline. Other clinical outcomes, such as diagnosis of psychomotor or neurodevelopmental delay or quality of life, were not reported in any trial.

Although not clearly clinical outcomes, developmental test scores after follow-up periods of 3 to 12 months were reported in 3 fair-quality trials.[23,26,28] Two trials ($N = 428$ and 1657, respectively), including the Chilean

study with methodologic flaws mentioned earlier, found no statistically significant difference between groups on the Bayley Scales of Infant Development (Table 2). Differences between groups were small and ranged from 0.6 to 0.7 on mental development and 0.2 to 0.7 for psychomotor development.[26,28] One trial of children potentially at higher risk for IDA used the Griffiths scale to measure psychomotor development.[23] Although scores in both groups declined and were within normal limits at 24 months, they declined less in the iron-supplemented group (general quotient score at 24 months: −9.3 vs −14.7; $P = .04$).

Ten trials of iron supplementation in children reported inconsistent

TABLE 1 Good-Quality and Fair-Quality Trials of Iron Supplementation in Children Ages 6 to 24 Months on Hematologic and Growth Outcomes

Study, Year, Country, N, Duration; Quality	Risk Factors Reported	Interventions and Comparator	Outcomes: Supplementation Versus Control Groups					
			IDA (Hb <110 g/L and Iron Deficiency[a])	Anemia (Hb <110 g/L)	Iron Deficiency[a]	Hb	Serum Ferritin	Growth
Domellöf et al, 2001,[32] Sweden, N = 70, 3 mo; fair	Race: Not reported; Preterm and low birth weight infants excluded	A. Placebo from 4 to 6 mo and iron supplement from 6 to 9 mo of age (n = 34) B. Placebo from 4 to 9 mo (n = 36)	No effect (numbers not reported)	—	—	117.1 vs 114.4 g/L; P = NS	47.3 vs 22.9 μg/L; P < .001	Weight at 9 mo: 8.9 vs 8.9 kg (P = NS)
Geltman et al, 2004,[24] United States, N = 284, 3 mo; fair	Race: 55% vs 48% black; Preterm and low birth weight infants excluded	A. Oral multivitamin drops, 10 mg of iron/d B. Multivitamin drops without iron	8% (11/138) vs 8% (11/144) anemic and had 2 other abnormal hematologic values; RR: 1.04 (95% CI: 0.47–2.33)	22% (31/138) vs 19% (27/144); RR: 1.20 (95% CI: 0.76–1.90)	78% (108/138) vs 84% (121/144) had 1 abnormal hematologic value indicative of iron deficiency; RR: 0.93 (95% CI: 0.83–1.04)	117 vs 117 g/L; P = NS	32.0 vs 29.2 μg/L; P = NS	—
Gill et al, 1997,[25] United Kingdom and Ireland, N = 302, 11 mo; fair	Race: not reported; Preterm and low birth weight infants excluded	A. Iron-fortified formula B. Noniron-fortified formula C. Cow's milk	—	11% vs 13% vs 33%[b]	6% vs 22% vs 43%[b]	121.5 vs 117.7 vs 111.4 g/L; P = .006[c]	25.1 vs 15.3 vs 11.0 μg/L; P < .001	Weight: 11.1 vs 11.1 vs 11.3 kg (P = NS); Length: 78.9 vs 79.1 vs 80.3 cm (P = NS)
Lozoff et al, 2003,[26] Chile, N = 1657, 6–12 mo; fair	Race: not reported; Preterm and low birth weight infants excluded	A. Multiple interventions with varying iron concentrations B. No iron supplementation	3.1% (34/1114) vs 22.6% (116/514); RR: 0.14 (95% CI: 0.09–0.20)	4.3% (48/1123) vs 25.8% (138/534); RR: 0.17 (95% CI: 0.12–0.23)	26.5% (286/1081) vs 51.3% (273/532); RR: 0.52 (95% CI: 0.45–0.59)	123.6 vs 115.6 g/L; P < .001	14.0 vs 8.7 μg/L; P < .001	Weight: 10.0 vs 10.1 kg (P < .05); Weight for age (z score): 0.05 vs 0.13 (P = NS) Length: 74.7 vs 75.1 cm (P < .001); Length for age (z score): −0.27 vs −0.15 (P < .01) Head circumference: 46.7 vs 47.0 cm (P < .001)
Makrides et al, 1998,[27] Australia, N = 62, 6 mo; fair	Race: not reported; Preterm and low birth weight infants excluded	A. High-iron weaning diet B. Control weaning diet	0 vs 0	0 vs 19.2% (5/26); RR: 0.07 (95% CI: 0.00–1.15)	3.9% (5/36) vs 7.7% (2/26); RR: 1.81 (95% CI: 0.38–8.60)	120 vs 115 g/L; P = NS	26 vs 35 μg/L; P = NS	—
Morley et al, 1999,[28] United Kingdom, N = 428, 9 mo; fair	Race: not reported; Preterm and low birth weight infants excluded	A. Iron-fortified formula, 1.2 mg iron/L B. Unfortified formula, 0.9 mg iron/L C. Cow's milk	—	—	—	126 vs 120 vs 119 g/L; P < .01 for A versus C, P < .05 for A versus B	21.7 vs 13.1 vs 14.3 μg/L; P < .0001 for A versus B and A versus C	Weight: 11.4 vs 11.3 vs 11.4 kg (P = NS); Length: 82.3 vs 82.3 vs 82.6 cm (P = NS)

TABLE 1 Continued

Study, Year, Country, N, Duration; Quality	Risk Factors Reported	Interventions and Comparator	Outcomes: Supplementation Versus Control Groups					
			IDA (Hb <110 g/L and Iron Deficiency[a])	Anemia (Hb <110 g/L)	Iron Deficiency[a]	Hb	Serum Ferritin	Growth
Szymlek-Gay et al, 2009,[29] New Zealand, N = 225, 5 mo; good	Race: 84% vs 78% vs 76% white	A. ≥2 portions of red meat, 1.3 mg of iron per portion; B. Iron-fortified milk, 1.5 mg iron/100 g; C. Cow's milk	No difference between groups (data only reported in a figure)	—	—	118.6 vs 121.5 vs 120.2 g/L; P = NS	32.8 vs 43.5 vs 29.9 µg/L; effect size in fortified milk group 1.68 (95% CI: 1.27–2.24)	No effect on growth
Williams et al, 1999,[23] other publication: Daly et al, 1996,[22] United Kingdom, N = 92, 10–12 mo; fair	Race: 74% white, 24% black, 2% Asian; Receiving income support: 59%; Preterm and low birth weight infants excluded	A. Iron-supplemented formula, 1.2 mg iron/100 mL; B. Cow's milk	—	At 18 mo of age: 2% (1/46) vs 33% (15/46); RR: 0.07 (95% CI: 0.01 to 0.48)	—	—	30.5 vs 15.9 µg/L; P = .001	No effect on growth (data not shown)

Two trials were omitted from the table due to poor-quality rating (Yalçin et al, 2000[30] and Yeung and Zlotkin, 2000[31]). Hb, hemoglobin; NS, not significant.

a Iron deficiency was defined variably as serum ferritin <10 µg/L,[25, 27, 30] <15 µg/L,[24] or <12 µg/L in addition to 1 of 2 other hematologic indicators.[26]

b RR not calculable based on data reported.

c Groups differed significantly at baseline.

findings for incidence of IDA, iron deficiency, and anemia, as well as changes in hemoglobin and serum ferritin (Table 1 [poor-quality studies were omitted from tables]).[22,24–32]

Iron supplementation was not found to influence the incidence of IDA in 4 good- or fair-quality studies (N values ranged from 62 to 284).[24,26,27,29,32] One study, the aforementioned larger Chilean study (N = 1657) with a high incidence of IDA in the control group (22.6%) and methodologic flaws regarding randomization, reported a significant benefit (RR: 0.14 [95% CI: 0.09–0.20]).[26] Overall, the studies reported ranges of IDA from 0% to 8% for those in the supplementation group and 0% to 22.6% in the placebo group.

For incidence of iron deficiency, 2 fair-quality studies with high incidences in the control groups suggest a significant benefit of supplementation. These findings included 1 study (N = 302) that compared iron-fortified formula with noniron-fortified formula and cow's milk (6% vs 22% vs 43%)[24] and the large (N = 1657) Chilean study (26.5% vs 51.3%; RR: 0.52 [95% CI: 0.45–0.59]).[26] Three other studies found no difference in rates of iron deficiency,[24,27,30] including the only study conducted in the United States (RR: 0.94 [95% CI: 0.74–1.20]).[24] Overall, the studies reported rates of iron deficiency ranging from 3.9% to 78% for those in the supplementation group and from 7.7% to 84% in the placebo group.

Six trials (5 fair-quality and 1 poor-quality; N values ranged from 62 to 1657) reported the effect of supplementation on the rate of anemia (variably defined as hemoglobin <100–110 g/L, sometimes in combination with other abnormal iron measures).[22–27,30] Two of these studies (from the United States and the United Kingdom) found no clear benefit from supplementation.[24,25] The remainder, including the large Chilean study,

TABLE 2 Bayley Scales of Infant Development Outcomes in Iron Supplementation Studies

Study, Year, Country, N; Quality	Duration	Risk Factors Reported	Interventions and Comparator	Mental Development Index	Psychomotor Development Index
Lozoff et al, 2003,[26] Chile, N = 1657; fair	6 mo	Race: Not reported; Preterm and low birth weight infants excluded	A. Multiple interventions with varying iron concentrations B. No iron supplementation	103.9 vs 104.6; P = NS	96.7 vs 97.5; P = NS
Morley et al, 1999,[28] United Kingdom, N = 428; fair	9 mo	Race: Not reported; Preterm and low birth weight infants excluded	A. Iron-fortified formula, 1.2 mg of iron/L B. Unfortified formula, 0.9 mg of iron/L C. Cow's milk	93.9 vs 94.5 vs 96.2; P = NS	94.8 vs 94.6 vs 93.6; P = NS

One trial omitted from table due to poor-quality rating (Yalçin et al, 2000[30]). NS, not significant.

reported significant benefits, with RRs ranging from 0.07 (95% CI: 0.01–0.48)[26] to 0.14 (95% CI: 0.09–0.20).[23] However, variability in the definitions of anemia, the unknown mix of baseline risk of children enrolled, and the variation in control group rates across these studies (from 13% to 33%) limit the interpretability of the findings for US populations. Overall, the studies reported rates of anemia ranging from 0% to 22% for those in the supplementation group and from 13% to 33% in the placebo group.

In addition, hemoglobin results were reported in 8 studies,[24–30,32] with small differences between groups; 3 were significant.[25,26,28] Nine studies reported ferritin concentrations, with conflicting results.[22–30,32]

Harms of Routine Iron Supplementation in Children Ages 6 to 24 Months

None of the studies of iron supplementation reported serious harms, including accidental overdose or withdrawals due to adverse events. Five studies reported on adherence to the assigned regimen and found no impact based on iron content. In some cases, however, the control group was preferred (eg, cow's milk over fortified or unfortified formula).[24,28–31]

In 1 fair-quality trial, no clinically significant adverse events thought to be related to study interventions were reported.[25] No differences in rate of gastrointestinal adverse events in toddlers consuming iron-fortified milk and those consuming unfortified milk were found in

a good-quality trial (2% vs 2%; RR: 1.0 [95% CI: 0.9–11]).[29] No other studies reported the incidence of gastrointestinal adverse events.

Screening for IDA

Benefits and Harms of Screening Asymptomatic Children Ages 6 to 24 Months for IDA

As in previous reviews,[16,17] no studies evaluating the benefits or harms of screening programs for asymptomatic children ages 6 to 24 months for IDA were found.

Benefits and Harms of Treatment of IDA in Children Ages 6 to 24 Months

No new studies of oral iron treatment of IDA in infants and children 6 to 24 months of age were found. Of the studies included in the previous reviews, only 1 study (N = 110) met our current criteria.[35] This study was rated as poor quality due to baseline differences in age and unclear reporting of methods. Improved growth velocity and hemoglobin and ferritin levels were found, but no differences were reported in Denver Developmental Screening Test psychomotor development outcomes compared with control subjects.

No newly published studies reporting harms of iron treatment in children ages 6 to 24 months were found. One older randomized controlled trial (N = 334), published in 1991[36] and not included in the previous reviews, reported no differences between children receiving iron treatment and those receiving placebo in overall

incidence or incidence of specific adverse events, including gastrointestinal events.

Association Between a Change in Iron Status and Improvement in Child Health Outcomes in Populations Relevant to the United States

No studies met the established criteria to evaluate an association between improvement in impaired iron status and child health outcomes in populations relevant to the United States.

One poor-quality and 2 fair-quality supplementation studies provided evidence regarding changes in iron status and measures of growth or development scale scores in children with normal iron status at baseline.[22,25,30] Two fair-quality studies (Table 3) found statistically significant changes in iron status measures but no differences between groups in measures of weight or height after 9 and 18 months.[22,25] A poor-quality trial found large numerical (but nonsignificant) differences in hemoglobin and serum ferritin levels and a significant difference in transferrin saturation, but no differences in weight, height, or head circumference outcomes or in neurodevelopmental outcomes based on the Bayley Scales of Infant Development.[30]

DISCUSSION

As in the previous USPSTF reviews,[16,17] we found no evidence regarding the effects of routine iron supplementation in young children on

TABLE 3 Association Between Change in Iron Status and Health Outcomes

Study, Year, Country, N; Quality	Duration	Intervention Groups	Baseline Iron Status	Follow-up Iron Status	Mean Change in Iron Status	Health Outcomes
Daly et al, 1996,[22] United Kingdom, N = 100; fair	18 mo	A. Iron-fortified formula (n = 41)	A vs B Hemoglobin: 119 vs 120 g/L	A vs B Hemoglobin: 124 vs 118 g/L	A vs B Hemoglobin: 5.0 vs −2.0 g/L (P < .0001)	A vs B No difference between groups in weight for age, weight for height, or height for age (data not shown)
		B. Cow's milk (n = 43)	Serum ferritin: 33.2 vs 34.6 μg/L	Serum ferritin: 32.4 vs 14.9 μg/L	Serum ferritin: 0.8 vs −19.7 μg/L (P < .0001)	
Gill et al, 1997,[25] N = 406; United Kingdom and Ireland; fair	9 mo	A. Iron-fortified formula (n = 264)	A vs B vs C Hemoglobin: 118.9 vs 116.6 vs 114.4 μg/L	A vs B vs C Hemoglobin: 121.5 vs 117.7 vs 111.4 μg/L	A vs B vs C Hemoglobin: 2.6 vs 1.1 vs −3.0 μg/L (A versus B and C, P < .01)	A vs B vs C Weight, mean change from baseline: 11.1 (3.2) kg vs 11.1 (3.1) kg vs 11.3 (3.0) kg (P = NS for all comparisons)
		B. Formula without iron fortification (n = 85)	Serum ferritin: 41.6 vs 42.3 vs 31.9 μg/L	Serum ferritin: 25.1 vs 15.3 vs 11.0 μg/L	Serum ferritin: −16.5 vs −27.0 vs −20.9 μg/L (A vs B and C, P < .001)	Length, mean change from baseline: 79.1 (11.3) cm vs 78.9 (11.5) cm vs 80.3 (12.2) cm (P = NS for all comparisons)
			Serum iron: 14.9 vs 13.9 vs 12.5 mmol/L	Serum iron: 14.4 vs 12.9 vs 10.0 mmol/L	Serum iron: −0.5 vs −1.0 vs −2.5 mmol/L (A vs B and C, P = .04)	
		C. Cow's milk (n = 57)	Total iron-binding capacity: 61.1 vs 59.0 vs 64.9 mmol/L	Total iron-binding capacity: 63.0 vs 70.3 vs 73.2 mmol/L	Total iron binding capacity: 1.9 vs 11.3 vs 8.3 mmol/L (A vs B and C, P = .05)	

One poor-quality trial was omitted from the table (Yalçin et al, 2000[30]). NS, not significant.

diagnosis of psychomotor or neurodevelopmental delay or quality of life, and the evidence regarding developmental test scores after 3- to 12-month follow-up periods (although not clearly clinical outcomes) does not indicate important differences.[23,26,28,30] We found no evidence of important or clear benefit in growth outcomes, which is consistent with the findings of a recent meta-analysis of 21 randomized controlled trials that included studies from any country.[18]

Although the study findings are not consistent, the evidence from 10 trials of iron supplementation in children indicates no benefit in terms of incidence of IDA, anemia, or hemoglobin; the findings were inconsistent regarding incidence of iron deficiency and serum ferritin concentrations.[22–32]

Some of the variation in findings may have been due to inadequate sample sizes for specific outcomes. This situation is often ideal for pooling studies to gain statistical power; in this case, however, we found both clinical and methodologic

heterogeneity and did not combine the studies. For example, there was important variability in the definitions of IDA, anemia, and iron deficiency (mostly unknown baseline risk of children enrolled) and wide variation in control group rates across these studies. Although the prevalence rates of iron deficiency in the United States are currently estimated at 8%[5–7], control group rates in these studies ranged from 13% to 33%, such that generalizability of these findings to the US population is unclear. Studies that did find a benefit generally had higher rates of iron deficiency in the control groups compared with studies which found no benefit, suggesting that baseline risk is important in determining who will benefit from supplementation, in terms of preventing iron deficiency. An additional factor potentially contributing to variability was the use of cow's milk as a control in several studies; use of cow's milk is considered a risk factor for IDA and is advised against before 12 months of age by the American Academy of

Pediatrics, and the Centers for Disease Control and Prevention.[2,37,38]

In addition, 1 of the largest studies included in the review that consistently found statistically significant results supporting supplementation for most hematologic values was conducted in Chile and had a high incidence of hematologic values in the control groups. This study, which initially randomized children to receive low- or high-iron supplementation, broke randomization, leading to baseline differences between the groups.[26]

Harms of routine iron supplementation in children were rarely reported, and supplementation did not result in higher rates in studies reporting harms. Although an older meta-analysis of 28 studies (randomized controlled trials and cohort studies) found a slightly increased risk of diarrhea with iron supplementation (RR: 1.1 [95% CI: 1.0–1.2]),[39] the majority of studies were conducted in developing countries, and the age of the populations ranged from 2 days to 14 years.

As in the previous reports, evidence regarding the benefits and harms of screening for IDA in children ages 6 to 24 months is absent. Similarly, we found only very limited evidence regarding the benefits and harms of IDA treatment that is generalizable to children ages 6 to 24 months in the United States. Based on this evidence, benefits were shown only for some iron status measures in the short term. Previous USPSTF reports concluded that there was no evidence regarding the relative harms of treatment. This update identified only 1 additional study, which indicated no differences between children receiving iron supplementation and placebo in the incidence of overall or specific adverse events, including gastrointestinal events.[36]

The potential for long-term benefit of preventing IDA in young children presumes that improvement in iron status is associated with good long-term clinical outcomes, such as normal growth and neurodevelopment. Evidence capable of showing this specific association was extremely limited and did not support a clear association between change in iron status and differences in growth or neurodevelopment.

Limitations of our report include restricting inclusion of studies published in English and studies conducted in developed countries or studies in developing countries where the population enrolled was similar to the population of the United States, particularly in terms of rates of malnutrition, hemoparasite burden, and general socioeconomic status. A number of studies of iron supplementation and treatment that were conducted in developing countries were excluded.[40–46] Malnourishment, very low socioeconomic status, and/or presence of parasitic endemic diseases were common in the included populations in these studies. Also excluded were studies of iron supplementation that enrolled children aged <6 months[47–50]; this population was outside the scope of the review.

Good-quality, randomized controlled trials of routine supplementation, screening programs, and treatment of IDA in children 6 to 24 months of age, with adequate sample sizes for key iron status and clinical health outcomes, are needed. Such trials should clearly report prognostic baseline characteristics of enrolled children, details of interventions, longer term benefits (particularly developmental outcomes using appropriate neurodevelopmental tests), and harms, and the studies should use appropriate controls (ie, not cow's milk). In addition, these studies should report neurodevelopmental diagnoses rather than test scores.

CONCLUSIONS

Expanded and better research is needed to assess the benefits and harms of routine iron supplementation and screening to prevent IDA in young children in developed countries. At present, the limited evidence indicates no benefits in growth and neurodevelopmental test scores with supplementation, and hematologic outcomes are variably affected. The benefits and harms of treatment are largely unclear, as is the association between improvement in IDA or iron deficiency and clinical outcomes.

ACKNOWLEDGMENTS

REFERENCES

1. World Health Organization. Iron deficiency anaemia: assessment, prevention and control: a guide for programme managers. Available at: www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf. Accessed February 3, 2015

2. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep.* 1998;47(RR-3):1–29

3. Griffin IJ, Abrams SA. Iron and breastfeeding. *Pediatr Clin North Am.* 2001;48(2):401–413

4. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. *Am J Clin Nutr.* 2007;85(4): 931–945

5. Bamberg R. Occurrence and detection of iron-deficiency anemia in infants and toddlers. *Clin Lab Sci.* 2008;21(4): 225–231

6. Brotanek JM, Gosz J, Weitzman M, Flores G. Secular trends in the prevalence of iron deficiency among US toddlers, 1976-2002. *Arch Pediatr Adolesc Med.* 2008; 162(4):374–381

7. Schneider JM, Fujii ML, Lamp CL, Lönnerdal B, Dewey KG, Zidenberg-Cherr S. Anemia, iron deficiency, and iron deficiency anemia in 12-36-mo-old children from low-income families. *Am J Clin Nutr.* 2005;82(6):1269–1275

8. Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics.* 2010;126(5): 1040–1050

9. Centers for Disease Control and Prevention (CDC). Iron deficiency—United States, 1999-2000. *MMWR Morb Mortal Wkly Rep.* 2002;51(40):897–899

10. Cusick SE, Mei Z, Freedman DS, et al. Unexplained decline in the prevalence of anemia among US children and women between 1988-1994 and 1999-2002. *Am J Clin Nutr.* 2008;88(6):1611–1617

11. Hay G, Sandstad B, Whitelaw A, Borch-Iohnsen B. Iron status in a group of Norwegian children aged 6-24 months. *Acta Paediatr.* 2004;93(5):592–598

12. Oti-Boateng P, Seshadri R, Petrick S, Gibson RA, Simmer K. Iron status and dietary iron intake of 6-24-month-old children in Adelaide. *J Paediatr Child Health.* 1998;34(3):250–253

13. US Preventive Services Task Force. Screening for iron deficiency anemia, including iron supplementation for children and pregnant women. Available at: www.uspreventiveservicestaskforce. org/uspstf/uspsiron.htm. Accessed February 3, 2015

14. McDonagh M, Blazina I, Dana T, Cantor A, Bougatsos C. *Routine Iron Supplementation and Screening for Iron Deficiency Anemia in Children Ages 6 to 24 Months: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. XXX.* AHRQ Publication No. XXX. Rockville, MD: *Agency for Healthcare Research and Quality.* In press

15. United States Preventive Services Task Force. US Preventive Services Task Force Procedure Manual. AHRQ Publication No. 08-05118-EF, July 2008. Available at: www. uspreventiveservicestaskforce.org/ uspstf08/methods/procmanual.htm. Accessed February 3, 2015

16. Oregon Evidence-based Practice Center. Screening for iron deficiency anemia in childhood and pregnancy: update of the 1996 U.S. Preventive Services Task Force Review. Evidence Synthesis No. 40. AHRQ Publication No. 06-0590-EF-1. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www. uspreventiveservicestaskforce.org/ uspstf06/ironsc/ironscrev.pdf. Accessed February 3, 2015

17. DiGuiseppi C, ed. Screening for iron deficiency anemia—including iron prophylaxis. *Guide to Clinical Preventive Services.* 2nd ed. Report of the US Preventive Services Task Force. Baltimore, MD: Williams & Wilkins; 1996

18. Vucic V, Berti C, Vollhardt C, et al. Effect of iron intervention on growth during gestation, infancy, childhood, and adolescence: a systematic review with meta-analysis. *Nutr Rev.* 2013;71(6): 386–401

19. Logan S, Martins S, Gilbert R. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. *Cochrane Database Syst Rev.* 2009(1):CD001444

20. Wang B, Zhan S, Gong T, Lee L. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. *Cochrane Database Syst Rev.* 2013(6):CD001444

21. United Nations Development Programme, Human Development Reports. Data. Available at: http://hdr. undp.org/en/statistics/. Accessed February 3, 2015

22. Daly A, MacDonald A, Aukett A, et al. Prevention of anaemia in inner city toddlers by an iron supplemented cows' milk formula. *Arch Dis Child.* 1996;75(1): 9–16

23. Williams J, Wolff A, Daly A, MacDonald A, Aukett A, Booth IW. Iron supplemented formula milk related to reduction in psychomotor decline in infants from inner city areas: randomised study. *BMJ.* 1999;318(7185):693–697

24. Geltman PL, Meyers AF, Mehta SD, et al. Daily multivitamins with iron to prevent anemia in high-risk infants: a randomized clinical trial. *Pediatrics.* 2004;114(1):86–93

25. Gill DG, Vincent S, Segal DS. Follow-on formula in the prevention of iron deficiency: a multicentre study. *Acta Paediatr.* 1997;86(7):683–689

26. Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. *Pediatrics.* 2003;112(4):846–854

27. Makrides M, Leeson R, Gibson R, Simmer K. A randomized controlled clinical trial of increased dietary iron in breast-fed infants. *J Pediatr.* 1998;133(4):559–562

28. Morley R, Abbott R, Fairweather-Tait S, MacFadyen U, Stephenson T, Lucas A. Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: a randomised trial. *Arch Dis Child.* 1999;81(3):247–252

29. Szymlek-Gay EA, Ferguson EL, Heath AL, Gray AR, Gibson RS. Food-based strategies improve iron status in toddlers: a randomized controlled trial12. *Am J Clin Nutr.* 2009;90(6): 1541–1551

30. Yalçin SS, Yurdakök K, Açikgöz D, Özmert E. Short-term developmental outcome of iron prophylaxis in infants. *Pediatr Int.* 2000;42(6):625–630

31. Yeung GS, Zlotkin SH. Efficacy of meat and iron-fortified commercial cereal to prevent iron depletion in cow milk-fed infants 6 to 12 months of age: a randomized controlled trial. *Can J Public Health.* 2000;91(4):263–267

32. Domellöf M, Cohen RJ, Dewey KG, Hernell O, Rivera LL, Lönnerdal B. Iron supplementation of breast-fed Honduran and Swedish infants from 4 to 9 months of age. *J Pediatr.* 2001;138(5):679–687

33. Jary S, Whitelaw A, Walløe L, Thoresen M. Comparison of Bayley-2 and Bayley-3 scores at 18 months in term infants

following neonatal encephalopathy and therapeutic hypothermia. *Dev Med Child Neurol.* 2013;55(11):1053–1059

34. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. The Bayley-III cognitive and language scales: how do scores relate to the Bayley II? *Arch Dis Child.* 2011;96 (suppl 1):A39–A40

35. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child.* 1986;61(9):849–857

36. Irigoyen M, Davidson LL, Carriero D, Seaman C. Randomized, placebo-controlled trial of iron supplementation in infants with low hemoglobin levels fed iron-fortified formula. *Pediatrics.* 1991; 88(2):320–326

37. American Academy of Pediatrics. Why formula instead of cow's milk. Available at: www.healthychildren.org/English/ages-stages/baby/feeding-nutrition/Pages/Why-Formula-Instead-of-Cows-Milk.aspx. Accessed February 3, 2015

38. American Academy of Pediatrics Committee on Nutrition. The use of whole cow's milk in infancy. *Pediatrics.* 1992; 89(6):1105–1109

39. Gera T, Sachdev HP. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ.* 2002;325(7373):1142

40. Lind T, Lönnerdal B, Stenlund H, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: effects on growth and development. *Am J Clin Nutr.* 2004; 80(3):729–736

41. Majumdar I, Paul P, Talib VH, Ranga S. The effect of iron therapy on the growth of iron-replete and iron-deplete children. *J Trop Pediatr.* 2003;49(2):84–88

42. Pollitt E, Saco-Pollitt C, Jahari A, Husaini MA, Huang J. Effects of an energy and micronutrient supplement on mental development and behavior under natural conditions in undernourished children in Indonesia. *Eur J Clin Nutr.* 2000;54(suppl 2):S80–S90

43. Olney DK, Pollitt E, Kariger PK, et al. Combined iron and folic acid supplementation with or without zinc reduces time to walking unassisted among Zanzibari infants 5- to 11-mo old. *J Nutr.* 2006;136(9):2427–2434

44. Villalpando S, Shamah T, Rivera JA, Lara Y, Monterrubio E. Fortifying milk with ferrous gluconate and zinc oxide in a public nutrition program reduced the prevalence of anemia in toddlers. *J Nutr.* 2006;136(10):2633–2637

45. Akman M, Cebeci D, Okur V, Angin H, Abali O, Akman AC. The effects of iron deficiency on infants' developmental test performance. *Acta Paediatr.* 2004;93(10): 1391–1396

46. Engstrom EM, Castro IR, Portela M, Cardoso LO, Monteiro CA. Effectiveness of daily and weekly iron supplementation in the prevention of anemia in infants. *Rev Saude Publica.* 2008;42(5):786–795

47. Abdelrazik N, Al-Haggar M, Al-Marsafawy H, Abdel-Hadi H, Al-Baz R, Mostafa AH. Impact of long-term oral iron supplementation in breast-fed infants. *Indian J Pediatr.* 2007;74(8):739–745

48. Berglund S, Westrup B, Domellöf M. Iron supplements reduce the risk of iron deficiency anemia in marginally low birth weight infants. *Pediatrics.* 2010; 126(4). Available at: www.pediatrics.org/cgi/content/full/126/4/e874

49. Sankar MJ, Saxena R, Mani K, Agarwal R, Deorari AK, Paul VK. Early iron supplementation in very low birth weight infants—a randomized controlled trial. *Acta Paediatr.* 2009; 98(6):953–958

50. Ziegler EE, Nelson SE, Jeter JM. Iron supplementation of breastfed infants from an early age. *Am J Clin Nutr.* 2009; 89(2):525–532