Effects of iron supplementation in nonanemic pregnant women, infants, and young children on the mental performance and psychomotor development of children: a systematic review of randomized controlled trials

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ABSTRACT
Background: Uncertainty exists regarding the effects of iron supplementation on neurodevelopmental outcomes in the absence of anemia.

Objective: Our objective was to evaluate the effects of iron supplementation in nonanemic pregnant women and in nonanemic healthy children aged <3 y on the mental performance and psychomotor development of children.

Design: In this systematic review, MEDLINE, EMBASE, and The Cochrane Library were searched through December 2009 for randomized controlled trials (RCTs).

Results: None of 5 RCTs individually showed a beneficial effect of iron supplementation during early life on the Mental Developmental Index of the Bayley Scales of Infant Development at different ages throughout the first 18 mo. Meta-analysis of 3 RCTs (n = 561) showed that, compared with placebo, supplementation with iron had no significant effect on children’s Mental Developmental Index at ≈12 mo of age (weighted mean difference: 1.66; 95% CI: -0.14, 3.47). Three of 5 RCTs showed a beneficial effect of iron supplementation on the Psychomotor Development Index of the Bayley Scales of Infant Development at different ages and on the basis of the results of 17 randomized controlled trials (RCTs) that involved 3646 participants, it was concluded that iron supplementation has a modest effect on mental development, particularly for intelligence quotient (IQ) scores in children aged >7 y and in those who are initially anemic or iron-deficient anemic. No effects of iron supplementation on the Bayley Mental Developmental Index and motor development score were shown. The limitations of this review include wide variations among included trials and a lack of specified inclusion criteria for the participants. Martins et al (5) published a protocol in the Cochrane Review that aimed to determine the effects of iron supplementation during early life on neurodevelopmental outcomes in the absence of anemia.

In 2005, one systematic review with a meta-analysis was performed that aimed to determine the effects of iron supplementation on mental and motor development in children (4). On the basis of the results of 17 randomized controlled trials (RCTs) that involved 3646 participants, it was concluded that iron supplementation has a modest effect on mental development, particularly for intelligence quotient (IQ) scores in children aged >7 y and in those who are initially anemic or iron-deficient anemic. No effects of iron supplementation on the Bayley Mental Developmental Index and motor development score were shown. The limitations of this review include wide variations among included trials and a lack of specified inclusion criteria for the participants. Martins et al (5) published a protocol in the Cochrane Review that aimed to assess the effects of iron sup-

INTRODUCTION
Iron plays a fundamental role in many functions of the body, which include the following: oxygen transport, production of ATP (the main energy storage and transfer molecule in the cell), DNA synthesis, mitochondrial function, and protection of cells from oxidative damage (1). Iron is also required for the activity of a number of enzymes involved in specific brain functions, such as myelination and synthesis of the neurotransmitters serotonin (tryptophan hydroxylase) and dopamine (tyrosine hydroxylase), a precursor to adrenaline and norepinephrine (2).

Iron deficiency with or without anemia continues to be extremely common in infants and children, particularly in the developing world, but also in some sectors of industrialized countries (ie, in lower socioeconomic groups). An association between iron deficiency and psychomotor development in infants and children has been addressed in a number of studies of different study design and are reviewed elsewhere (2, 3). In brief, these reviews concluded that there is a causal relation between severe iron-deficiency anemia and poor measures of psychomotor development or cognitive function. In contrast, the causal relation between moderate iron-deficiency anemia and adverse effects on psychomotor and mental functions is less clear. The most questionable is the effect of iron deficiency on neurodevelopmental outcomes in the absence of anemia.

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plementation provided to infants beginning before 1 y of age on measures of psychomotor development or cognitive function. Unfortunately, a full review was not published until the date of preparation of this manuscript. Given these considerations, the present review was undertaken to update data on the effects of iron supplementation during pregnancy and/or in early life on the mental performance and psychomotor development of children. Our objective was to systematically evaluate the effects of iron supplementation in nonanemic pregnant women and nonanemic young children (<3 y old) on the mental and psychomotor development of children.

METHODS

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of this systematic review were followed (6).

Criteria for the consideration of studies for this review

Types of studies: All relevant RCTs that compared the effects of iron supplementation with the effects of no supplementation or placebo were eligible for inclusion.

Types of participants: Pregnant mothers who were not anemic at the start of supplementation and nonanemic healthy children aged 0–3 y were considered for inclusion. We excluded trials that dealt with iron supplementation in subjects with anemia.

Types of interventions: Studies that compared the effects of iron supplementation with the effects of placebo or no intervention were included.

Types of outcome measures: We evaluated any standardized measures of psychomotor development, cognitive function, and behavior in children.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 4, 2009; http://www.cochrane.org), MEDLINE (1966–2009; http://www.ncbi.nlm.nih.gov/pubmed/), and EMBASE (1980–2009; http://www.embase.com) databases were systematically searched up to December 2009. The reference lists of identified studies and key review articles, which included previously published reviews, were also searched for all studies that assessed the effects of iron supplementation on child neurodevelopment. No language restrictions were imposed.

The following search terms were used: iron supplementation, ferrous, mental, cognitive, psychomotor, development, intelligence, behavior, visual, prenatal, pregnancy, fetus, neonates, child, children, infants, toddlers, and preschoolers. The search strategy used both keywords and MeSH terms. No further limitations were made, to make the search as sensitive as possible. All the reviewers searched the databases independently.

Data collection and analysis

Selection of studies

We excluded studies if the title and abstract were not relevant; however, we obtained all potentially relevant studies if the abstract contained insufficient information to warrant exclusion. All areas of disagreement were discussed by the researchers to achieve consensus.

Data extraction and management

Data from each study were extracted by all the reviewers with the use of data extraction forms. After extraction, all data were compared to minimize the possibility of errors. Because the objective of our review was to compare solitary iron supplementation with no supplementation, data related to other intervention groups were not considered (eg, data related to infants fed iron and zinc or iron and multiple other micronutrients).

Assessment of risk of bias in included studies

The reviewers independently, but without being blinded to the authors or journal, assessed the risk of bias in the studies that met the inclusion criteria. We used the Cochrane Collaboration’s tool for the assessment of risk of bias, which includes the following criteria: adequacy of sequence generation, allocation concealment, and blinding of participants, personnel, and outcome assessors; addressing of incomplete outcome data; and selective outcome reporting. In all cases, an answer of “yes” indicates a low risk of bias, and an answer of ”no“ indicates a high risk of bias (7).

Measures of treatment effect

The data were analyzed with the use of Review Manager (RevMan, version 5.0; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes (with 95% CIs). For dichotomous data, we intended to calculate risk ratios (RRs) with 95% CIs.

Dealing with missing data

We assessed pooled data with the use of available case analysis [ie, an analysis in which data are analyzed for every participant for whom the outcome was obtained, rather than intention-to-treat analysis with imputation (8)]. One RCT reported the total number of children but did not provide the number of children in the experimental and control groups at various time intervals (9). For missing data, an assumption about the sample size was made (by division of the total number of subjects into 2 groups).

Assessment of heterogeneity

We used a chi-square test to assess heterogeneity and the Higgins $I^2$ statistic to determine the percentage of total variation across studies due to heterogeneity (10). A value of 0% indicates no observed heterogeneity, and larger values show increased heterogeneity. For simplicity, if heterogeneity ($I^2 >50\%$) was not shown, we present the results of the fixed effects model only.

Assessment of reporting biases

To test for publication bias, we planned to use a test for asymmetry of the funnel plot proposed by Egger et al (11). However, the publication bias was not formally assessed with the use of a funnel plot because of the small number of studies (<10) included in the analyses of primary outcome measures.
RESULTS

Included studies

Our search identified 7 trials that were eligible and met our predefined inclusion criteria. Key characteristics of the included trials are summarized in Table 1. Two publications (12, 13) described the same study population but reported different outcomes. The study population consisted of 430 nonanemic, pregnant Australian women who received 20 mg elemental iron or placebo orally daily from 20 wk gestation until delivery.

Five RCTs addressed iron supplementation in infants and children (9, 14–17). Two of those studies were conducted in Canada, one in the United Kingdom, one in Turkey, and one in Indonesia. The age of participants at enrollment ranged from 0 to 9 mo. Three RCTs (15–17) provided iron in the form of syrup or suspension. The dosages of ferrous sulfate in these studies were 7.5 mg/d, 10 mg/d, and 1 mg \( \cdot \) kg\(^{-1} \cdot \) d\(^{-1} \), respectively. In 2 RCTs (9, 14), iron-fortified formula was compared with nonfortified formula. The concentration of iron fortification of formula ranged from 1.2 mg/L (14) to 12.8 mg/L (9). The duration of the intervention ranged from 3 to 15 mo.

Authors of the included trials used different measures to estimate mental and psychomotor development. In 5 RCTs, the Bayley Scales of Infant Development (BSID) were used, either version I (9, 17) or version II (14–16). The BSID are among the most commonly used scales, and they assess language (receptive and expressive), visual problem-solving skills, behavior, and motor skills (fine and gross) in young children. A Mental Developmental Index (MDI) score and Psychomotor Development Index (PDI, a measure of motor competence) score are derived from the results.

### Table 1: Characteristics of included trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population at enrollment (location)</th>
<th>Intervention (iron)</th>
<th>Control</th>
<th>Duration of intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supplementation in children</strong></td>
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<tr>
<td>Friel et al, 2003 (15)</td>
<td>Term breastfed infants (Canada)</td>
<td>Ferrous sulfate 7.5 mg/d (( n = 42 ))</td>
<td>Placebo (( n = 35 ))</td>
<td>From 1 to 6 mo of age (5 mo)</td>
<td>BSID II (MDI, PDI) assessed from ages 12 to 18 mo</td>
</tr>
<tr>
<td>Lind et al, 2004 (16)</td>
<td>Healthy singleton infants (Indonesia)</td>
<td>Ferrous sulfate 10 mg/d (( n = 163/170 ))</td>
<td>Placebo (( n = 164/170 ))</td>
<td>From 6 to 12 mo of age (6 mo)</td>
<td>BSID II (MDI, PDI) and behavioral rating scale at age 12 mo</td>
</tr>
<tr>
<td>Moffatt et al, 1994 (9)</td>
<td>Healthy infants aged &lt;2 mo from very low income families (Canada)</td>
<td>Iron-fortified formula: 12.8 mg/L (( n = 113 ))</td>
<td>Regular formula: 1.1 mg/L (( n = 112 ))</td>
<td>15 mo</td>
<td>BSID I (MDI) and 2 factors of the Infant Behavior Record (test affect and task orientation) at age 6, 9, 12, and 15 mo</td>
</tr>
<tr>
<td>Morley et al, 1999 (14)</td>
<td>Healthy children aged 9 mo (UK)</td>
<td>Iron-fortified formula: 1.2 mg/L (( n = 133/162 ))</td>
<td>Unfortified formula with iron: 0.9 mg/L (( n = 135/165 )); unmodified cow milk (( n = 160/166 ))</td>
<td>From 9 to 18 mo</td>
<td>BSID II (MDI, PDI) at age 18 mo</td>
</tr>
<tr>
<td>Yalcın et al, 2000 (17)</td>
<td>Healthy iron-sufficient infants (Turkey)</td>
<td>Ferrous sulfate 1 mg ( \cdot ) kg(^{-1} \cdot ) d(^{-1} ) (( n = 7/11 ))</td>
<td>No supplementation (( n = 9/13 ))</td>
<td>From 6 to 9 mo (3 mo)</td>
<td>BSID I (MDI, motor score) at age 9 mo</td>
</tr>
<tr>
<td><strong>Supplementation in pregnant women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parsons et al, 2008 (13)</td>
<td>Pregnant women (Australia)</td>
<td>Iron (20 mg/d)</td>
<td>Placebo</td>
<td>From 20 wk of gestation until delivery</td>
<td>Child behavior and temperament with the use of the Strengths and Difficulties Questionnaire and the Short Temperament Scale for Children at age 6–8 y</td>
</tr>
<tr>
<td>Zhou et al, 2006 (12)</td>
<td>Pregnant women (Australia)</td>
<td>Iron [( n = 216 ) assigned to receive iron (20 mg/d); ( n = 153 ) included in IQ analysis; ( n = 151 ) included in behavior analysis]</td>
<td>Placebo (( n = 214 ) assigned to receive placebo; ( n = 149 ) included in IQ analysis; ( n = 149 ) included in behavior analysis)</td>
<td>From 20 wk of gestation until delivery</td>
<td>IQ (Stanford-Binet Intelligence Scale) at age 4 y</td>
</tr>
</tbody>
</table>

1 BSID I and BSID II, Bayley Scales of Infant Development versions 1 and 2; MDI, Mental Developmental Index; PDI, Psychomotor Development Index; IQ, intelligence quotient.
Excluded studies

We excluded 40 trials. (An additional figure and table can be found under “Supplemental data” in the online issue.) The most common reasons for exclusion were an ineligible study design, the inclusion of participants with anemia at enrollment, and the use of iron supplementation in combination with other micronutrients.

Risk of bias in included studies

The results of the assessment of risk of bias of the included trials (methodologic quality assessment) are shown in Table 2.

Although the included trials had some methodologic limitations, in general the methodologic quality was good. The major limitation was incomplete outcome data (>20% lost to follow-up). The risk of selective outcome reporting was unclear because of insufficient information (ie, unavailability of study protocols of the included trials, which would allow comparison of pre-specified and reported outcomes).

Supplementation in early infancy

BSID

In 5 included RCTs (9, 14–17), the BSID was used to assess infants at different ages throughout the first 18 mo of life.

MDI

None of the individual RCTs showed a beneficial effect of iron supplementation on the MDI at any time point studied (Figure 1). Pooled results of 3 RCTs (9, 15, 16) (n = 561) that assessed MDI scores at ~12 mo showed that the iron-supplemented group had a mean MDI score that was 1.66 points higher than that of the control group; however, the difference between groups was of borderline statistical significance (WMD: 1.66, 95% CI: −0.14, 3.47). No heterogeneity was shown (χ² = 0.47; P = 0.79; I² = 0%), as shown in Figure 2.

PDI

Three RCTs showed a beneficial effect of iron supplementation on the PDI at some time points, whereas 2 did not (Figure 1).

Among studies that provided iron in the form of syrup or suspension, one small study that involved 46 subjects (15) reported a higher mean PDI score at 13 mo in infants supplemented with iron at a dose of 7.5 mg/d from 1 to 6 mo of age compared with the placebo group. Similarly, a larger study (16) (n = 327) reported a higher mean PDI score at 12 mo in infants supplemented with iron at a dose of 10 mg/d from 6 to 12 mo of age compared with the placebo group. In contrast, one small RCT (17) that involved only 16 children documented that the

**TABLE 2**

Methodologic quality summary: review of authors’ judgment about each methodologic quality item for each included study

<table>
<thead>
<tr>
<th>Study</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding</th>
<th>Incomplete outcome data addressed</th>
<th>Selective outcome reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friel et al, 2003 (15)</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Lind et al, 2004 (16)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Moffatt et al, 1994 (9)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Morley et al, 1999 (14)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Parsons et al, 2007 (13)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Yalçın et al, 2000 (17)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Zhou et al, 2006 (12)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

1 In all cases, an answer of “yes” indicates a low risk of bias, and an answer of “no” indicates a high risk of bias.

**FIGURE 1.** Iron supplementation in early infancy compared with control. The Bayley Scales of Infant Development–Mental Developmental Index (MDI) and Psychomotor Development Index (PDI) at different ages throughout the first 18 mo of life. The first 5 lines list trials with iron-fortified formula (F) with different amounts of iron fortification (mg/L); lines 6–8 list trials in which iron was provided in the form of syrup or suspension (mg · kg⁻¹ · d⁻¹ or mg/d) (references 9 and 14–17). IV, inverse variance.
administration of iron sulfate at a dose of 1 mg · kg⁻¹ · d⁻¹ from 6 to 9 mo of age compared with no administration did not have an effect on the Bayley motor score at 9 mo.

Two RCTs evaluated the effect of iron fortification of formula. One trial (9) showed that the administration of a fortified formula with an iron content of 12.8 mg/L compared with regular formula to healthy term infants from very-low-income families in Canada resulted in higher mean PDI scores at 9 and 12 mo of age; however, no difference in mean PDI scores between groups was observed at 6 and 15 mo of age. Another trial (14), which involved 268 healthy children in the United Kingdom, documented that the administration of a fortified formula with an iron content of 1.2 mg/L from 9 to 18 mo of age did not have an effect on the PDI score at 18 mo.

A pooled analysis of data from 3 RCTs (n = 561) (9, 15, 16) that assessed PDI scores at ≥12 mo of age showed significant improvement in scores in the iron-supplemented group compared with the control group (WMD: 4.21; 95% CI: 2.31, 6.12). No significant heterogeneity was shown (I² = 33%) (Figure 2).

Behavior

One RCT (9) assessed behavior with the use of the Infant Behavior Record. This trial showed that iron supplementation had no effect on either test affect (social responsiveness to examiner, fearfulness, tension, emotional tone, and endurance) or task orientation (object orientation, goal directedness, attention span, and reactivity) at any assessment time (ie, 6, 12, and 15 mo). Another RCT (16) used the behavioral rating scale. No significant difference in behavioral rating scale scores between the iron supplementation and placebo groups was shown.

Prenatal supplementation

One RCT by Zhou et al (12) evaluated whether iron supplementation during pregnancy influences the IQ or behavior of the child. The IQ was measured with the Stanford-Binet Intelligence Scale and behavior was assessed with the Strength and Difficulties Questionnaire at the age of 4 y (n = 302). Compared with the placebo, iron supplementation of pregnant women did not change the mean IQ of the children (109 ± 11, P = 0.98). Of note, only 302 children of the 430 originally randomized pregnant women were available for the analysis. Zhou et al (12) also reported that there was no difference in mean scores for behavioral difficulties between children of mothers in the iron and placebo groups. Interestingly, however, the percentage of children with an abnormal behavior score was slightly higher in the group of children whose mothers received iron than in the group of children whose mothers received placebo (16% compared with 8%; RR: 1.97; 95% CI: 1.03, 3.80; P = 0.037).

The same population was studied by Parsons et al (13) at 6–8 y of age. Of the original 433 children born to the 430 randomized pregnant women, 264 (61%) participated in the follow-up. Child behavior and temperament were assessed with use of the Strengths and Difficulties Questionnaire and the Short Temperament Scale for Children. There were no statistically significant differences in mean behavior and temperament scores between children of mothers in the iron and placebo groups. However, the percentage of children with an abnormal, teacher-rated, peer problems subscale score was higher in the group of children whose mothers received iron than in the group of children whose mothers received placebo (8% compared with 2%; RR: 3.7; 95% CI: 1.06, 12.91; P = 0.026).

DISCUSSION

Major findings

The objective of this systematic review of RCTs was to provide some resolution to the uncertainty regarding the effects of iron supplementation during pregnancy and/or early in life on the psychomotor and mental development of children. Only trials in which subjects were not iron deficient were included. This review shows that iron supplementation of infants may moderately increase the PDI score, with the effect most evident at ≥12 mo of age. Conversely, there is no evidence that iron supplementation of infants has a beneficial effect on the mental development or behavior of children. Studies that examined the influence of prenatal iron supplementation of pregnant women did not show an effect on either the IQ or behavioral status of their children, except for a higher incidence of children with teacher-rated peer
problems at school. In the interpretation of this potentially worrying finding, it is important to consider the high attrition rate (>50%) and very wide CI around this result.

The aim of this review was to focus specifically on nonanemic infants/children or pregnant women. Thus, our results may be applicable only to such a population. These results should be interpreted with caution because of the limited evidence available. However, our results do not exclude the potential benefit of iron supplementation. For example, our review showed that iron supplementation resulted in a better MDI score at 12 mo; however, this finding was of a borderline statistical significance. Our review also showed that iron supplementation resulted in a better PDI score at 12 mo. It remains an open question as to whether an increase in the PDI score by 4.2 points is clinically relevant. The BSID were designed to detect delayed development. These scales are not considered to be sensitive enough for the detection of subtle differences between infants and they may be inappropriate for the detection of differences in neurodevelopment (18). Yet if a difference exists, potential benefit is likely. Further larger trials may provide more definitive answers. If confirmed, these findings would be relevant to public health strategies aimed at the improvement of the neurodevelopment of children.

Most of the included trials were performed in industrialized countries. Thus, the generalizability of our results to less privileged, low-income settings is limited. In consideration of the fact that severe iron deficiency with anemia is very common in the developing world and is associated with altered neurodevelopment, different approaches may be needed in the 2 settings. Research needs for the establishment of effective programs for the control of iron deficiency and its consequences in children in low-income countries are under extensive discussion (19, 20).

Strengths and limitations of the review

Our search included 3 relevant databases, with no language restrictions. All the reviewers were involved in the data search and extraction, and the assessment of validity; therefore, the likelihood of reviewers’ error or bias was decreased. However, no attempt was made to identify unpublished studies, primarily because there is no systematic process for finding controlled trials that were conducted but not published. The inclusion of unpublished data lowers the risk of publication bias, defined as the failure to report results of a negative trial. The inclusion of unpublished data are not, however, without challenges and drawbacks, which have been fully reviewed elsewhere (21). One of the challenges is that the located trial data may be an unrepresentative sample of data from all related unpublished studies and thus, may introduce further bias. Another problem related to publication bias is selective outcome reporting, which we were unable to assess because of insufficient information to permit judgment.

The strength of our review, which limits the bias, is the inclusion of RCTs only. Randomization is the only means to control for unknown and unmeasured differences between comparison groups as well as those that are known and measured. Such a study design is particularly important for the assessment of mental and psychomotor development when confounders such as social class, parental education, living standards, and maternal age could affect developmental scores. To control for all known confounders, a large number of subjects would be required. The use of individual participant data, as recently performed to assess whether supplementation with long-chain polyunsaturated fatty acids has an effect on the BSID (22), would be another option and provide greater power.

Any meta-analysis is only as good as the constituent studies. Potential limitations of included trials include no intention-to-treat analysis and a small sample size in some trials. All the included trials varied in terms of study population, duration, and amount of iron supplementation; outcomes and the times of their assessment were also different. Whereas most of the included trials used the BSID, the assessments, with few exceptions, were made at different time points. Consequently, the generalizability of the results is limited.

Relation of findings to those of similar studies

This review differs in some ways from the systematic review published by Sachdev et al (4). First, we included trials in which supplementation was introduced early (before 3 y of age), whereas Sachdev et al (4) included trials that involved infants, toddlers, and older children. Second, we focused our review on healthy, nonanemic subjects. In contrast, Sachdev et al (4) included both preventive and therapeutic studies, although the reviewers did not specify the type of participants to be included. They concluded that iron supplementation has a modest effect on mental development, particularly on IQ scores in children older than 7 y and in initially anemic or iron-deficient anemic subjects. However, they reported there is no convincing evidence of an effect of iron supplementation on the mental development of children younger than 27 mo. The latter conclusion is consistent with the results of the present review.

Possible mechanisms

The exact mechanisms that underlie the relation between iron deficiency and altered psychomotor development remain uncertain. Possible explanations have been extensively discussed in earlier studies and reviews. In brief, it has been postulated that a lack of iron during critical periods of brain development may lead to abnormalities in the metabolism of neurotransmitters, decreased myelination, and alterations in energy metabolism of the brain, and consequently, to alterations in psychomotor development and cognition (2, 5, 23).

Implications for practice

In the absence of clear evidence, it is reasonable to follow recommendations made by scientific organizations, such as the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (3, 24). The committee recommends that until more data are available, measures should be taken to prevent iron deficiency. These measures include the promotion of exclusive breastfeeding, the use of iron-fortified formulas when formula feeding is needed, the postponement of the introduction of whole cow milk as the main drink until the end of the first year of life, and the promotion of consumption of complementary foods rich in iron.
Implications for research

Well-designed intervention studies that evaluate the role of iron supplementation of nonanemic pregnant women and/or children are still needed to determine the effects of such supplementation on the mental and psychomotor development of children.

Conclusions

Only a few studies have addressed the effects of iron supplementation during pregnancy and/or in early life on psychomotor development and cognitive performance. Iron supplementation of infants may positively affect the psychomotor development of children but may not influence their mental development and behavior.

The authors’ responsibilities were as follows—HS (guarantor) and MR: analyses and first draft of the manuscript; HS: final report; and HS, MR, and AC: data interpretation, initial protocol of the review, literature search, study selection, methodologic quality assessment, data extraction, and approval of final report. None of the authors declared a conflict of interest.

REFERENCES