Benefits of Iron Supplementation for Low Birth Weight Infants

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CONTEXT
Iron is an essential micronutrient that plays a critical role in many cellular functions and processes, including growth and development. This systematic review was performed to examine the effects of iron supplementation on hematologic iron status, growth, neurodevelopment, and adverse effects in low birth weight (LBW)/premature infants.

METHODS/DATA SOURCES
The Cochrane Library, Medline, and PubMed databases were searched from inception to June 2011. Searches were limited to include only articles written in English. Studies were eligible for inclusion if they involved infants who were of LBW or premature of <35 weeks and received enteral or parenteral iron supplementation. Studies were excluded if there was no definite length of treatment available, or if supplementation was combined with erythropoietin treatment.

Data were extracted by 3 independent reviewers. Each reviewer used a standardized data collection form to increase uniformity and reduce bias. The following information data were extracted: First author; year of publication; journal; eligibility criteria; definition of premature or LBW; number of cases and control; hematological data before and after iron supplementation; iron dose; duration of supplementation; growth status; and adverse effects.

RESULTS
A total of 2065 articles were identified, but only 15 articles met the inclusion criteria and were included in the systematic review.

The studies included were published between 1960 and 2010 and included LBW infants aged from birth to 80 days. The number of LBW infants in the iron supplementation group ranged from 16 to 90, with most studies having 20 to 40 infants per iron supplementation group. Iron was most commonly given orally or as an iron-fortified formula. In 1 study only, iron was given by intramuscular injection. The duration of iron supplementation varied considerably, ranging from 1 week up to 18 months.

The majority of studies employed a method of randomization (10/15; 66.7%), had similar group characteristics at baseline (9/15; 60%), specified eligibility criteria (13/15; 86.7%), provided point estimates and measures of variability for the primary outcome measures (13/15; 86.7%), and included an intention-to-treat analysis (12/15; 80.0%). Only 6/15 (40%) studies provided any definitive information about blinding. Meta-analyses of the extracted data were not performed because mean values were not available, or doses were not adjusted by body weight in the majority of the studies identified.

Effect of iron supplementation on hematologic parameters
All but 1 study reported on the effects of iron supplementation on hematologic measures of iron status. The majority of studies reported that iron supplementation significantly increased hematologic measures of iron status relative to control. Specifically, Hammond et al. reported that premature infants treated for 2-4 days with intramuscular iron-dextran had significantly higher hemoglobin concentrations and hematocrit values from 3 months of age onwards and significantly higher erythrocyte counts from 5 months of age onwards compared with premature infants in the control group.

In another study, Lundstrom et al. found that LBW infants treated for approximately 6 months with an oral iron supplement (2 mg/kg/day) had significantly higher hemoglobin, serum ferritin, MCV, and transferrin saturation levels at 3 months compared with the control group. Iwai et al. similarly reported that LBW infants fed an iron-fortified formula (8 mg/L) for 6 months had significantly higher hemoglobin, serum ferritin, and MCV concentrations than control infants fed human milk only.

In a non-placebo-controlled study, Arnon et al. found that premature infants fed enteral iron (5 mg/kg/day) from 2 weeks of age to 8 weeks of age had significantly higher hemoglobin, reticulocyte, iron, and ferritin concentrations compared with premature infants fed the same iron dose from 4 to 8 weeks of age.

A small number of studies included in the systematic review
found that iron supplementation had no significant effect on hematologic measures of iron status relative to control. Franz et al. reported that early iron supplementation (2 to 4 mg/kg/day once enteral feeding was tolerated) had no significant impact on indicators of iron status in infants with a birth weight < 1301 grams.

Effect of Iron supplementation on the prevalence of Iron deficiency and Iron-deficiency anemia

All controlled studies that examined the prevalence of Iron deficiency (ID) and/or Iron-deficiency anemia (IDA) found that their prevalence was lower in infants who received iron supplementation compared with infants who did not receive iron supplementation. Higher iron doses were found to be associated with decreased prevalence of ID and/or IDA. Only 1 study (Brozovic et al.) found no obvious benefit of iron supplementation on the prevalence of ID and/or IDA.

Effect of Iron supplementation on growth and neurodevelopment

Five studies examined the effect of iron supplementation on growth, whereas only 2 studies examined the effect on neurodevelopment. None of the studies that examined growth-related variables: Growth rate, length, head circumference, and weight, found any effect of iron supplementation. With regards to neurodevelopment, Friel et al. found that iron supplementation did not improve cognitive development as measured using Griffiths’ Development Assessment, but Steinmacher et al. found that early supplementation (< 61 days of age) tended to improve neurocognitive and psychomotor development compared with late supplementation (≥ 61 days of age), as indicated by neurologic examination findings and Gross Motor Function Classification Scores.

Adverse effects of iron supplementation

None of the studies found any evidence that iron supplementation increased oxidative stress in LBW infants. The study conducted by Friel et al. was the only study to examine absorption of other nutrients with iron supplementation and found that both plasma zinc and copper concentrations were significantly higher for the group of infants who received high vs. normal iron supplementation. Three of the 5 studies that reported on neonatal morbidity found no differences between the control and treatment groups or dose-dependent effects of iron supplementation on the overall incidence of morbidity. The other 2 studies found that there was a tendency for there to be a higher prevalence of respiratory tract infections in the iron supplementation group compared with the control group or the high compared with the normal iron supplementation group. Arnon et al. reported that significantly more infants who started iron supplementation at 4 weeks of age required blood transfusions than infants who started iron supplementation at 2 weeks of age.

CONCLUSIONS

This review suggests that iron supplementation can improve indicators of hematologic iron status and reduce the occurrence of ID/IDA in LBW/premature infants. The benefits of iron supplementation on growth appear to be limited, at least in the short term (within 18 months of treatment), whereas there is insufficient evidence on the effects of iron supplementation on neurodevelopment or the occurrence of adverse events in this population.

COMMENTARY

In spite of the wide spread practice of administering iron supplements to LBW/premature infants, there were only 15 studies qualified to be included in this systemic review. The long-term benefits of iron supplementation remain uncertain. More randomized controlled trials are needed, using well-defined patient groups, aiming to determine if specific cohorts of LBW/premature infants are more likely to benefit from iron supplementation, and the optimal dose, timing, and duration of supplementation.

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