Enteral iron supplementation in preterm and low-birth-weight infants

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1. INTRODUCTION

Iron-deficiency anaemia is the most prevalent nutritional deficiency worldwide, especially in women of childbearing age and pre-school children. Although anaemia is a global problem, it is more prevalent in under-resourced settings in Africa and South-East Asia. The highest prevalence rates have been found in preschool-age children (47.4%), and the greatest number of individuals affected are non-pregnant (468 million) and pregnant (56 million) women (1).

Adequate nutrition of women before pregnancy is essential to ensure optimal birth weight of the infant (2). Anaemia, especially in areas of malaria transmission, retards intrauterine growth, resulting in low birth weight, which is a major contributor to neonatal mortality (3, 4). Research has shown that anaemia and iron deficiency are associated with adverse effects on cognitive, socio-emotional and motor development of children (2). Iron deficiency during the first 6–12 months of life can persist during childhood and affect functioning in adulthood. Iron deficiency has also been associated with changes in brain morphology, neurochemistry and bioenergetics, resulting in delayed development of the central nervous system (5).

This review (6) aimed to evaluate the effects of prophylactic enteral iron supplementation on growth and neural development in preterm and low-birth-weight infants. Another objective of the review was to determine whether iron supplementation improves haematological parameters and prevents morbidity and mortality from other causes.

2. METHODS OF THE REVIEW

The review authors analysed studies comparing enteral iron supplementation versus no supplementation or versus different regimens of enteral iron supplementation (dose, duration and timing of initiation). Subgroup analyses included evaluating the effects by type of milk-feeding, age of start of iron supplementation after birth, daily dose of supplemental iron administered, duration of supplementation, and gestational age as well as birth weight of infants.

The authors included randomized and quasi-randomized controlled trials that had compared preterm (before...
37 weeks of gestation) or low-birth-weight (<2500 g) infants receiving enteral iron supplementation (?1 mg/kg/day) with a control group (placebo or ? 1 mg/kg/day of iron). Infants receiving concurrent treatment with erythropoietin were excluded.

The primary outcomes measures were neural development and anthropometric measurements at 12 months or less, two years or less, and five years or less. Secondary outcomes measures included changes in haemoglobin concentration, mean corpuscular volume, serum ferritin concentration, transferrin saturation and total iron-binding capacity grouped according to age at the beginning of supplementation (6–8 weeks, 3–4 months, 6–9 months, and 12 months).

Anaemia, mortality, chronic lung disease, retinopathy of prematurity, hospitalization duration and readmission were also evaluated as outcomes.

The authors identified trials through the Cochrane Neonatal Review Group, the Cochrane Central Register of Controlled Trials, the Oxford Database of Perinatal Trials and non-electronic searches. Eligibility of trials and data extraction were performed separately by each author following the standard methods of the Cochrane Neonatal Review Group. Data were synthesized using risk ratios (RRs), risk differences (RDs) and weighted mean differences (WMDs).

3. RESULTS OF THE REVIEW

Twenty-six studies involving 2726 infants were included in the review. Most of the included trials had assessed iron supplementation versus placebo or no supplementation, and had tested doses between 2 mg/kg/day and 4 mg/kg/day. Some included studies evaluated doses of 10–44 mg/kg/day. The comparisons were enteral iron supplementation versus no iron supplementation, early versus late commencement of supplementation, a high dose versus a low dose as well as duration of supplementation.

Neurodevelopmental outcome, the main objective of this review was reported in only two studies (neither of them being a randomized controlled trial). Both studies failed to show any effect of supplementation.

Regarding secondary outcomes, there was a slight improvement in haemoglobin and ferritin concentrations in supplemented infants at 2 months of age compared with infants receiving no supplementation. All other outcomes showed no effect of the intervention or were inconclusive.

4. DISCUSSION

Available evidence is insufficient to assess the effect of enteral iron supplementation on the neurodevelopmental and long-term growth outcomes for preterm and low-birth-weight infants. In both groups of infants, iron supplementation marginally improved haemoglobin levels and iron stores and reduced the risk of developing iron-deficiency anaemia in those receiving supplements.

4.1 Applicability of the findings

There is currently insufficient evidence to determine the effect of oral iron supplementation on neural development and growth of preterm and low-birth-weight infants. The majority of the included studies found an improvement in haemoglobin and ferritin concentrations when iron was initiated at 2 months of age. The analysis failed to identify any benefit from doses higher than 2 mg iron/kg/day. It is important to note that during the period through which the included studies were conducted (1952 to 2010), there have been changes in not only the iron compounds used as supplements, but also the procedures for handling low-birth-weight and preterm infants.

The findings of this review should be interpreted with caution owing to limitations in terms of data quantity and comparability of the studies included: the studies were heterogeneous in terms of population,
interventions, doses, exclusion criteria, iron compounds used, the outcomes reported and methods of reporting results. The review authors graded the quality of the studies to be between fair and poor. Only eight out of 26 had adequate methods of allocation concealment and only eight had documented completion rates higher than 80%. The doses of iron varied from 2 mg/kg/day to 44 mg/kg/day and were calculated based on the mean birth weight. There were also differences with respect to administration of vitamin E and cobalt.

A serious limitation of the review is the actual amount of iron received by the infants, especially in terms of the impact on haematological outcomes. The data analysed in this review included infants that had received blood transfusions, even before being enrolled in a study. Some infants received blood transfusions during the study, whereas in certain studies a recent transfusion was an exclusion criteria.

4.2 Implementation of the intervention

The presence of anaemia in the mother is known to increase the risk of prematurity and low birth weight when maternal haemoglobin levels are below 95 g/L. Preterm infants are at risk of developing anaemia mainly due to two additional reasons, namely less time to develop intrauterine iron reserves and a rapid growth rate after birth (7, 8). Adverse effects of anaemia and iron deficiency on neurological development that may occur during infancy were irreversible in iron-deficient children followed during infancy, adolescence and early adulthood. Some evidence also suggests multi-causality for the poor motor and neural development since iron deficiency usually occurs in the context of poverty and food insecurity (9).

4.3 Implications for research

There is a need for additional research on how different iron compounds, administered as a supplement or as part of a food (infant formula), affect iron absorption and lead to different health outcomes. The iron compounds administered orally are absorbed according to their oxidation state, particle size and solubility. Iron compounds used for supplementation include sulfate, polynamate, ferric ammonium citrate, edetate, elemental or non-identified forms of iron. The bioavailability of these compounds varies greatly. The inclusion of iron in an infant formula also renders the iron less available than the same compound administered alone. Those two factors significantly define iron utilization and could affect results on neural development, growth and haematological outcomes.

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