Enteral Iron Supplementation in Preterm or Low Birth Weight Infants: A Systematic Review and Meta-analysis

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abstract

BACKGROUND AND OBJECTIVES: Iron is needed for growth and development of infants globally, but preterm and low birth weight (LBW) infants are at risk for severe iron deficiencies. To assess the effect of enteral iron supplementation on mortality, morbidity, growth, and neurodevelopment outcomes in preterm or LBW infants fed human milk. Secondary objectives were to assess the effect on biomarkers and dose and timing.

METHODS: Data sources include PubMed, Embase and Cochrane Library databases to March 16, 2021. Study Selection includes controlled or quasi experimental study designs. Two reviewers independently extracted data.

RESULTS: Eight trials (eleven reports; 1093 participants, 7 countries) were included. No trials reported mortality. At latest follow-up, there was little effect on infection (very low certainty evidence, 4 studies, 401 participants, relative risk [RR] 0.98, 95% confidence interval [95% CI] 0.56 to 1.73, $I^2 = 0.00\%$) and necrotising enterocolitis (3 studies, 375 participants, RR 1.47, 95% CI 0.68 to 3.20, $I^2 = 0.00\%$). There was an increase in linear growth (length) (moderate certainty evidence, 3 studies, 384 participants, mean difference 0.69 cm, 95% CI 0.01 to 1.37, $I^2 = 0\%$) but little effect on weight, head circumference, or cognitive development. There was an improvement in anemia (moderate certainty evidence, 2 studies, 381 participants, RR 0.25, 95% CI 0.10 to 0.62, $I^2 = 0.00\%$) but no effect on serum ferritin. Limitations include heterogeneity in the included studies.

CONCLUSIONS: There are important benefits for human milk-fed preterm and LBW infants from enteral iron supplementation. However, more randomized control trials are required to improve the certainty of evidence.

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Drs Manapurath and Gadapani Pathak, and Mr Chowdhury conceptualized and designed the study, drafted the initial manuscript, designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript; Drs Manapurath, Gadapani Pathak, Sinha, Upadhyay, Choudhary, Mazumdar, Taneja, and Bhandari, Mr Chowdhury, and Mr Chandola coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Iron is an essential nutrient that has a key role in the growth and development of infants globally. Preterm and low birth weight (LBW) infants have high demand for iron because of their low endowment of iron stores at birth, early-onset erythropoiesis, iatrogenic blood loss, and catch up growth.[1–3]

In 2012, a Cochrane systematic review reported that iron supplementation to preterm and LBW infants increased hemoglobin levels, improved iron stores, and reduced anemia when compared with no supplementation.[4] A more recent systematic review from 2019 reported that long-term iron supplementation (>8 weeks) improved iron status and reduced iron deficiency anemia in late infancy, compared with a shorter duration.[5] However, to our knowledge, there have been no systematic reviews that have assessed the effects of iron supplementation to preterm and LBW infants on mortality, morbidity, growth, and neurodevelopment outcomes. The optimum timing and duration of iron supplementation also remain unclear.

We conducted this review to evaluate the effect of enteral iron supplementation compared with no iron supplementation on mortality, morbidity, growth, and neurodevelopment among preterm or LBW infants who were fed mother's own milk or donor human milk. Our secondary objectives were to determine: (1) the effect on biomarkers (such as iron stores, anemia) and (2) the effect of different doses and timing.

METHODS

This review was registered in PROSPERO (CRD42021238738).[6] Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol (PRISMA-P) guidance was followed.[7]

Search

Electronic databases were searched to March 16, 2021. We searched Cochrane Central Register of Controlled Trials in the Cochrane Library via the Cochrane Register of Studies Online (CRSO); PubMed, and Embase using search terms listed in the Appendix 1 and we used no restrictions on the language of the articles. We also searched reference lists of the articles identified.

Two review authors (R.M. and B.P.) independently screened all the titles and abstracts identified by the search strategy. Disagreements were resolved by discussion or referring to a third review author (R.C.). Screening and full-text review of the articles were managed using the web-based software, Covidence.[8] We extracted data using modified Cochrane Effective Practice and Organization of Care Group data collection checklist.[9] Characteristics of the included and excluded studies are in Appendices 5 and 6.

Inclusion and Exclusion Criteria

We selected all randomized controlled trials (RCTs) and quasi-randomized trials which examined the impact of enteral iron supplementation or the effect of different doses, duration, and timing of initiation of iron supplementation on mortality, morbidity, growth, neurodevelopmental, and biomarker outcomes in preterm or LBW infants who were fed on mother's own milk or donor's human milk. Outcome definitions can be found in Appendix 3. We excluded studies where infants received erythropoietin.

Statistical Analysis

For each outcome, studies were pooled at the latest follow-up if more than 1 study was available. If a single study reported an outcome, the individual study effect size was reported. The unit of analysis was the infant.

We followed methods as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[10] We used the relative risk (RR) and mean difference (MD) as our outcome estimate measure for categorical and continuous outcomes respectively. We used adjusted estimates for pooling and if adjusted estimates were not available, unadjusted estimates were used. The fixed-effect meta-analysis (inverse variance method) was used to combine data when studies were estimating the same underlying treatment effects. High heterogeneity was defined as an I^2 value greater than 50%.[11] In cases of high heterogeneity, a random-effects model, and Restricted Maximum Likelihood Methods were used. The Cochrane "risk of bias (ROB)" tool and ROB in nonrandomized studies of Interventions tool were used to assess the risk of bias.[7] Two review authors (B.P. and R.M.) independently assessed the certainty of the evidence using the GRADE approach.[12]

We also conducted a prespecified subgroup analysis by gestational age (<32 weeks; very preterm births) and birth weight (<1500 g; very low birth weight).

RESULTS

We identified 1195 records. 8 trials (11 reports) examined the effect of iron supplementation versus no iron supplementation (Appendix 2).[13–20] Five trials enrolled very LBW or very preterm infants.[16–20] Five RCTs had high ROB,[13,14,16–18] and 3 had low ROB (Appendix 4).[15,19,20] The median dose of iron supplementation was 2.20 mg/kg per day (1.97–2.55 mg/kg per day) and iron supplementation

commenced between 14 and 56 days of postnatal age. The mean (SD) duration of supplementation was 81 (57) days, the median (IQR) duration of supplementation was 53 (40–98) days. We also identified 3 trials that examined the effect of high dose enteral iron supplementation (3.4–7.1 mg/kg per day) versus low dose iron supplementation (2.1–3.6 mg/kg per day).[14,21,22] We also identified 4 trials which examined the effect of early (within 2 weeks of postnatal age) compared with late (6 to 8 weeks of postnatal age) initiation of iron supplementation.[23–26] We identified no studies comparing the short and long duration of iron supplementation.

Iron Supplementation Versus No Iron Supplementation

No trials reported mortality as an outcome. Four studies (n = 401) reported data on infection at the latest follow-up (4, 8, and 9 weeks).[13,18,19] There was very low certainty evidence suggesting little or no effect on infection risk (RR 0.98, 95% CI 0.56 to 1.73, I^2 = 0.00%) (Table 1, Appendix 7, 8, and 11).

Three studies (n = 375) reported on necrotizing enterocolitis (NEC) at 4, 8 and 9 weeks (latest follow-up).[18,19] There was very low certainty of evidence suggesting little or no effect (RR 1.47, 95% CI 0.68 to 3.20, I^2 = 0.00%) (Table 1, Appendix 7 and 11).

Two studies (n = 238) reported on enteral iron intolerance at 8 weeks (latest follow-up).[13,17] There was very low certainty evidence suggesting little or no effect on enteral feed intolerance with RR 1.05 (95% CI 0.49 to 2.27, I^2 = 0.00%) (Table 1, Appendix 7 and 11).

Five studies (n = 574) reported on weight at the latest follow-up (8, 26, 36, and 183 weeks).[13,18–20,27] There was moderate certainty evidence suggesting little or no difference in weight among iron supplementation infants (MD 35.31 g, 95% CI −64.53 to 135.15 g, I^2 = 3.5%) (Table 1, Appendix 7 and 11).

Three studies13,20,27 (n = 384) reported on length at latest follow-up (8, 26, and 183 weeks) There was moderate certainty evidence of increase in length (MD 0.69 cm (95% CI 0.01 to 1.37, I^2 = 0%,) (Table 1, Appendix 7 and 11).

Three studies (n = 385) reported on the head circumference at the latest follow-up (8, 26, and 183 weeks).[13,20,27] There was low certainty evidence of little or no effect on head-circumference (MD −0.09 cm, 95% CI −0.4 to 0.21, I^2 = 6.68%) (Table 1, Appendix 7 and 11).

One study (n = 199) reported on cognitive outcomes at the latest follow-up, ie, 365 weeks.[28] There was very low certainty evidence suggesting no effect on cognitive development (RR 0.31, 95% CI 0.09 to 1.02) (Table 1, Appendix 7 and 11).

One study (n = 185) reported on behavior outcomes at the latest follow-up (365 weeks).[28] There was very low certainty evidence suggesting no effect on behavior (RR 0.80, 95% CI 0.22 to 2.87) (Table 1, Appendix 7 and 11).

Five studies (n = 506) reported on hemoglobin levels among infants at the latest follow-up (8, 26, and 183 weeks).[13–15,18,20] There was moderate certainty evidence suggesting an increase in hemoglobin level (MD 4.79 g/l, 95% CI 2.90 to 6.69, I^2 = 35.08%) (Table 1, Appendix 7 and 11).

Seven studies (n = 648) reported on serum ferritin at latest follow-up (4, 8, 20, and 26 weeks).[13–15,17,18,20] We found very low certainty evidence suggesting little or no effect on serum ferritin (MD 7.41 ng/mL, 95% CI −1.46 to 16.28, I^2 = 98%) (Table 1, Appendix 7 and 11).

Two studies (n = 381) reported on anemia at latest follow-up (26 weeks).[15,20] There was moderate certainty evidence suggesting decrease in anemia (RR 0.25, 95% CI 0.10 to 0.62, I^2 = 0.00%) (Table 1, Appendix 7 and 11).

In the studies which included very LBW and very preterm infants, there was very low certainty of evidence of increase in ferritin level (MD 5.23 ng/mL, 95% CI 1.73 to 8.73, I^2 = 32.14%).[18–20] There was little or no effect of iron supplementation on other iron markers (hemoglobin), growth (length, weigh, and head circumference), or morbidity (sepsis, NEC, enteral feeding intolerance) (Appendix 9 and 10).

Sensitivity analyses excluding studies that gave blood tranfusions and total parenteral nutrition to infants showed little change to the results (Appendices 14 and 15).

Timing and Dose

Five studies examined the effect of early (within 2 weeks of postnatal age) compared with late (6 to 8 weeks of postnatal age) iron supplementation.[17,23–26] Three studies (n = 228) reported on ferritin concentration among infants at the latest follow-up (8, 12, and 26 weeks).[23–25] There was very low certainty evidence of increase in ferritin concentration (MD 18.00 ng/mL, 95% CI 8.83 to 27.17, I^2 = 88.9%) and little or no effect on other biomarkers (hemoglobin), growth outcomes (length, weight, and head circumference) and morbidity outcomes (sepsis, necrotizing enterocolitis, cognitive

TABLE 1 Effect of Enteral Iron Supplementation Versus No Iron Supplementation on Morbidity, Growth, Neurodevelopment, and Biomarkers in LBW or Preterm Infants

Outcomes	No of Participants (studies)	Certainty of the Evidence (GRADE)	Relative Effect(95% CI)	Anticipated Absolute Effects	
				Risk With No Supplementation	Risk Difference With Iron Supplementation
Mortality	No studies	—	—	—	—
Morbidity	—	—	—	—	—
Sepsis prevalence latest follow up (7.5 [2.1][j] weeks; [8 (6–22)][k] weeks)	401 (4 RCTs)	⨁◯◯◯Very low[a]	RR 0.98 (0.56 to 1.73)	108 per 1000	2 fewer per 1000 (47 fewer to 79 more)
Necrotizing enterocolitis prevalence latest follow up (16 [1.7][j] weeks); (8 [4–36][k] weeks)	194 (3 RCTs)	⨁◯◯◯ Very low[a]	RR 1.47 (0.68 to 3.20)	49 per 1000	23 more per 1000 (16 fewer to 109 more)
Feed intolerance latest follow up (8 weeks)[j]	238 (2 RCTs)	⨁◯◯◯ Very low[b]	RR 1.05 (0.49 to 2.27)	158 per 1000	8 more per 1000(81 fewer to 201 more)
Iron biomarker					
Anemia prevalence at latest follow up (26 wk)	381 (2 RCTs)	⨁⨁⨁◯ Moderate[c]	RR 0.25 (0.10 to 0.62)	101 per 1000	231 fewer per 1000 (494 fewer to 322 fewer)
Hemoglobin at latest follow up (17.6 [9.1][j] weeks); (20 [8–26][k] weeks)	506 (5 RCTs)	⨁⨁⨁◯ Moderate[d]	—	Mean hemoglobin was 112.27 gm/l	MD 4.79 gm/l higher (2.9 higher to 6.69 higher)
Ferritin at latest follow up (26.7 [4.7][j] weeks); (12 [8–26][k] weeks)	607 (7 RCTs)	⨁◯◯◯ Very low[e]	—	Mean ferritin was 34.4 ng/mL	MD 7.41 ng/mL higher (1.46 lower to 16.28 higher)
Growth outcomes					
Wt at latest follow up (52.2 [74.10][j] weeks); (26 [8–36][k] weeks)	574 (5 RCTs)	⨁⨁◯◯ Low[f]	—	Mean wt was 7127.8 g	MD 35.31 g higher (64.53 lower to 135.15 higher)
Length at latest follow up (72.33 [96.26][j] weeks); (26 [8–183][k] weeks)	384 (3 RCTs)	⨁⨁⨁◯ Moderate[g]	—	Mean length was 83.04 cm	MD 0.69 cm longer (0.01 longer to 1.37 longer)
Head circumference at latest follow up (72.33 [96.26][j] weeks); (26 [8–183][k] weeks)	385 (3 RCTs)	⨁⨁◯◯ Low[h]	—	Mean head circumference was 45.4 cm	MD 0.09 cm lower (0.40 lower to 0.21 higher)
Neurodevelopment outcomes					
Cognitive at latest follow-up (365 wk)	199 (1 RCT)	⨁◯◯◯ Very low[i]	RR 0.31 (0.09 to 1.02)	100 per 1000	69 fewer per 1000 (91 fewer to 2 more)
Behavior and development at latest follow up (365 wk)	185 (1 RCT)	⨁◯◯◯ Very low[i]	RR 0.80 (0.22 to 2.87)	56 per 1000	11 fewer per 1000 (43 fewer to 106 more)

GRADE Working Group grades of evidence: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty, our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect; very low certainty, we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect. CI, confidence interval; MD, mean difference; RR, risk ratio; —, not available.

[a] Downgraded 3 levels for serious risk of bias and very serious imprecision (wide confidence interval, suboptimal sample size).

[b] Downgraded 3 levels for very serious risk of bias and very serious imprecision (wide confidence interval, suboptimal sample size).

[c] Downgraded the quality of evidence for imprecision by 1 level and the number of events was small (only 2 studies in which the intervention groups has been combined).

[d] Downgraded 1 level for serious risk of bias.

[e] Downgraded 3 levels for very serious risk of bias, serious imprecision (wide confidence interval), and serious inconsistency (high heterogeneity).

[f] Downgraded 2 levels for serious risk of bias and serious imprecision (wide confidence interval).

[g] Downgraded 1 level for serious risk of bias.

[h] Downgraded 2 levels for serious risk of bias and serious imprecision (wide confidence interval)

[i] Downgraded 3 levels for serious risk of bias, very serious imprecision (suboptimal sample size, wide confidence interval), and serious inconsistency (small number of studies).

[j] Mean (SD).

[k] Median (IQR).

neurodevelopment, and enteral feeding intolerance) (Appendix 12).

Three studies examined the effect of high dose of enteral iron supplementation (3.4 to 7.1 mg/kg per day) compared with low dose iron supplementation (2.1 to 3.6 mg/kg per day).[14,21,22] There was little or no effect on biomarkers (very low certainty evidence, hemoglobin MD 1.32 g/L, 95% CI −0.81 to 3.44, $I^2 = 48.16\%$, and ferritin MD 3.77 ng/mL, 95% CI −7.00 to 14.54, $I^2 = 91.34$). There was little or no effect of high dose of iron supplementation on growth outcomes (length, weight, and head circumference) and cognitive and behavioral neurodevelopment scores. There was no evidence on the effect of high dose enteral iron supplementation compared with low dose enteral iron supplementation on morbidity outcomes (sepsis, necrotizing enterocolitis, or enteral feeding intolerance) and mortality outcomes (Appendix 13).

DISCUSSION

Our systematic review found moderate certainty evidence of an increase in linear growth, an increase in hemoglobin concentration, and a reduction in the prevalence of anemia in human milk-fed preterm and LBW infants who received 2 to 4 mg/kg per day enteral iron supplementation. There was little or no effect on morbidity or neurodevelopment outcomes and no evidence on mortality. We found very low certainty evidence of increase in ferritin concentration when iron was provided at 2 weeks compared with 8 weeks postbirth. There was no effect of high dose of iron supplementation compared with low dose iron supplementation and no data on duration of supplementation.

We reported no benefits or harms from iron supplementation on morbidity outcomes (necrotizing enterocolitis, sepsis, or feed intolerance), including no increased risk of infection in iron supplemented infants in low- and middle-income countries.[4] However, the certainty of evidence for these outcomes was very low. Our review found moderate certainty evidence that iron supplementation improved linear growth but had no effect on weight and head circumference (low certainty). However, the growth data reported in our systematic review must be assessed with caution, as anthropometric measurement tools varied widely across settings. The effect of iron supplementation on growth outcomes is also known to be modified by levels of other micronutrients like zinc that vary widely across populations like those included in our review.[29] Our neurodevelopmental data were also of very low certainty. Our findings on biomarkers (hemoglobin and ferritin) were of higher certainty because of bigger study sizes and less heterogeneity and are similar to other systematic reviews.[4,5] Though variability of effect on ferritin and other measures of iron deficiency is reported in many studies as these biomarkers are influenced by levels of inflammation.[30–32]

The strengths of this review include our extensive literature search and inclusion of over 1000 participants in the included trials. Additionally, as the number of infants in the included studies was large, the statistical power was high for many primary outcomes. We also found low to moderate certainty evidence of important effects on linear growth outcomes and reduction in anemia levels. However, our review had marked heterogeneity for many outcomes, and we were not able to assess the impact on mortality outcomes.

Currently, the World Health Organization[33] and other organizations,[34,35] recommend that very LBW infants fed mother's own milk or donor human milk should be provided 2 to 4 mg/kg per day iron supplementation starting at 2 weeks until 6 months of age. Overall, the available evidence from our systematic review suggests important benefits for human milk-fed preterm and LBW infants from enteral iron supplementation. However, more RCTs are required to improve the quality of evidence and to understand the impact on mortality and morbidity outcomes. More RCTs are also needed to assess the effect of different types of enteral iron supplementation, the timing of initiation, duration of treatment, and dosage of supplementation.

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ABBREVIATIONS

CI: Confidence interval
GRADE: Grading of Recommendations Assessment, Development and Evaluation
LBW: low birth weight
MD: mean difference
RCT: randomized controlled trial
ROB: risk of bias
RR: relative risk
SD: standard deviation

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