Routine iron/folate supplementation during pregnancy: effect on maternal anaemia and birth outcomes

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CRD summary
The authors concluded that preventative iron supplementation significantly reduced the incidence of anaemia in mothers and low birthweight in infants. Differences between the included studies and the studies’ unclear quality mean the authors’ conclusions should be treated with caution.

Authors’ objectives
To investigate the effects of preventative iron supplementation on maternal anaemia and perinatal outcomes.

Searching
PubMed, The Cochrane Library and the World Health Organisation regional databases were searched up to June 2011 for articles in any language. Search terms were reported. References from selected studies and previous reviews were handsearched.

Study selection
Randomised or quasi-randomised trials that investigated pre-natal iron or iron plus folic acid for the prevention of anaemia compared to placebo or no intervention in pregnant women of any gestational age were eligible for inclusion. Studies of iron/iron-folate combined with other vitamin or mineral supplements were eligible for inclusion if iron/iron-folate was the only intervention difference between groups. Maternal outcomes eligible for inclusion were maternal anaemia at term, iron deficiency anaemia at term, maternal mortality, post-partum haemorrhage, need for blood transfusion and pre-eclampsia. Infant outcomes eligible for inclusion were low birthweight, weight at birth, preterm birth (in grams), perinatal death and congenital malformation. Studies from both developed and developing countries were eligible for inclusion. Studies of periconceptional or post-partum iron supplementation, iron or iron-folate supplementation in food or in forms other than oral supplementation or of iron in combination with other micronutrients were excluded. Studies of anaemic pregnant women were excluded. Studies with a very low grading in the quality assessment were excluded.

Included studies investigated iron or iron-folate supplementation in dosages ranging from 20mg to 300mg per day and started before 28 weeks gestation. Most studies evaluated iron supplementation alone; the other studies evaluated a combination of iron and folic acid supplementation. Studies were included from both developed and developing countries.

The authors did not state how the studies were selected for review.

Assessment of study quality
The quality of included studies was assessed according to Child Health Epidemiology Review Group adaptation of GRADE (Grading of Recommendations, Assessment, Development and Evaluation). Under these guidelines a study was awarded a score of high if it was a randomised controlled trial (RCT) or cluster RCT. One point was deducted for each study limitation such as inadequate sequence generation, allocation concealment or attrition higher than 20%. Where studies reported an intention-to-treat analysis or with strong statistically significant findings a 0.5 to 1.0 point increase was awarded. The overall evidence for primary outcomes was then summarised consistent with GRADE criteria according to the number of studies, consistenty of evidence, size of effect and statistical strength.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
For dichotomous outcomes, the number of events in each group was extracted and used to calculate relative risks (RR) with 95% confidence intervals (CI). For cluster randomised trials cluster adjusted relative risks with corresponding 95% CI were extracted. For continuous outcomes, data were extracted to calculate the mean differences and 95% CI.
Two reviewers independently extracted these data.

**Methods of synthesis**
For dichotomous outcomes, pooled relative risks with 95% CIs were calculated. For continuous outcomes, the weighted mean difference with 95% CIs were calculated. Statistical heterogeneity was assessed visually from forest plots and using the $X^2$ and $I^2$ statistics. Where significant statistical heterogeneity was found, a random-effects model was used for the meta-analyses. In the absence of significant heterogeneity a fixed-effect model was used.

Subgroup analyses were carried out for iron only and iron plus folate. Sensitivity analyses were carried out for frequency of dosage for the outcome of maternal anaemia.

**Results of the review**
The authors report that 30 studies were included for review (number of participants unclear). The studies that investigated the impact of iron on low birthweight were judged high quality. The studies of anaemia at term, pre-term birth, small-for-gestational age and perinatal mortality were judged moderate outcome-specific quality. Perinatal mortality was judged as low outcome-specific quality.

**Maternal outcomes:** Iron or iron-folate supplementation during pregnancy significantly reduced incidence of maternal anaemia by 69% compared to placebo or no supplementation (RR 0.31, 95% CI 0.22 to 0.44; $I^2=72%$; 18 studies; 8,665 participants). Subgroup analyses of iron only (RR 0.27, 95% CI 0.17 to 0.42) and iron plus folate (RR 0.38, 95% CI 0.18 to 0.80) also found significant benefits on maternal anaemia.

Frequency of dosage (intermittent supplementation versus daily supplementation) was not associated with any difference in the incidence of maternal anaemia. Iron/iron-folate supplementation significantly reduced the risk of iron deficiency anaemia at term (RR 0.44, 95% CI 0.28 to 0.68; $I^2=85%$; seven studies) and need for transfusion (RR 0.61, 95% CI 0.38 to 0.96; $I^2=0%$; three studies) compared to placebo or no supplementation. Iron supplementation did not significantly impact on severe anaemia at term or in the last two trimesters, post-partum haemorrhage or pre-eclampsia.

**Infant outcomes:** Iron or iron-folate supplementation during pregnancy was associated with significantly lower incidence of low birthweight than placebo or no supplementation (RR 0.80, 95% CI 0.71 to 0.90; $I^2=25%$; 11 studies; 9,397 participants). Iron or iron-folate supplementation was associated with significantly greater mean birthweight (WMD 42.18, 95% CI 9.27 to 75.09; $I^2=54%$; 13 studies) compared to placebo or no supplementation. There was no effect of iron supplementation on pre-term birth, perinatal mortality or small-for-gestational age.

**Authors’ conclusions**
Preventative iron supplementation significantly reduced the incidence of anaemia in mothers and low birthweight in infants.

**CRD commentary**
The review addressed a clear question with well defined inclusion criteria. Several relevant databases were searched. The search was not language restricted and this minimised the risk of language bias. It was unclear whether attempts were made to identify unpublished data and publication bias did not appear to have been assessed so it could not be ruled out. Data extraction was carried out independently in duplicate. It was unclear whether similar steps were taken during study selection and data extraction due to inadequate reporting.

A quality assessment was carried out but results for individual studies were not reported so it was not possible to assess the quality of each included study. The authors reported overall quality of evidence for some but not all outcomes. The overall grading of quality did not appear to reflect methodological quality of included studies. Hence the reliability of the data on which the meta-analysis was based was unclear. The authors did not report individual details of included studies so it was unclear whether the studies were sufficiently homogenous to justify combining in a meta-analysis. Significant statistical heterogeneity was found for many outcomes. The absence of study details made it unclear how the findings could be generalised across different dosages, frequencies and duration of supplementation or across different populations.

Given differences between included studies and the unclear quality of the included studies mean the authors’ conclusions should be treated with caution.
Implications of the review for practice and research

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further randomised controlled trials were needed on different delivery mechanisms of iron supplementation and comparison of weekly and daily dosage regimes.

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