Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis


CRD summary
The review concluded that daily prenatal use of iron substantially improved birth weight in a linear dose-response fashion, probably leading to a reduction in risk of low birth weight. An improvement in prenatal mean haemoglobin concentration linearly increased birth weight. These conclusions are likely to be reliable.

Authors’ objectives
To summarise evidence on the associations of maternal anaemia and prenatal iron use with maternal haematological and adverse pregnancy outcomes. To evaluate potential exposure-response relations of dose of iron, duration of use and haemoglobin concentration in the prenatal period with pregnancy outcome.

Searching
PubMed and EMBASE were searched to May 2012 without language or publication restrictions; a search strategy was reported. Reference lists of relevant articles were examined for further studies. Studies published only as abstracts were excluded.

Study selection
Randomised trials in pregnant women of daily oral iron (or iron and folic acid use) compared with placebo, no iron or no iron and folic acid were eligible. Trials of both supplementation and fortification were eligible. Studies had to examine maternal haematological, morbidity and birth outcomes (detailed definitions of what constituted these outcomes were reported). Prospective cohort studies that allowed examination of the association of baseline anaemia with birth outcomes were eligible. Anaemia was defined as haemoglobin less than 100g/L to haemoglobin less than 115g/L. Quasi-randomised trials, cross-sectional and case-control studies, studies of HIV-infected women or women with haemoglobinopathies and studies that evaluated only different doses of iron were excluded.

Most studies were conducted in high-income countries; others were in low- or middle-income countries. Most trials compared daily iron (with or without folic acid) with no iron or placebo. Iron doses ranged from 10mg to 900mg daily. Treatment durations ranged from seven to 30 weeks. Trial publication dates ranged from 1955 to 2011. Definitions of anaemia and assessment time points during pregnancy varied across the cohort studies.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
Randomisation, allocation concealment, blinding and losses to follow-up were evaluated and rated as adequate, unclear or inadequate. Trials were rated as being high quality when adequate for randomisation and allocation concealment plus either blinding or losses to follow-up were less than 20%. Methodological quality of cohort studies was assessed by comparing crude and adjusted estimates, controlling for the study confounders.

It appeared that two reviewers independently assessed study quality with disagreements resolved by discussion or by a third reviewer.

Data extraction
Data were extracted to obtain mean differences, relative risks (RR) or odds ratios (OR) with 95% confidence intervals (CI). Adjusted estimates (such as for confounders and study design) were extracted. Authors were contacted for missing data when necessary.

Two reviewers independently extracted data. Disagreements were resolved by discussion or by a third reviewer.

Methods of synthesis
Where there were at least five studies, meta-analyses were performed to calculate pooled weighted mean differences (WMD), relative risks or odds ratios with 95% confidence intervals. A random-effects model was used when heterogeneity $I^2$ values were more than 50% (and the Q statistic p-value was less than 0.1), otherwise a fixed-effect model was used.

A sensitivity analysis examined results for only high quality trials. The authors prespecified details of several subgroup and meta-regression analyses. Subgroup analyses were performed where there were at least 10 studies.

The possibility of publication bias was explored by visual inspection of funnel plots and by using Begg's and Egger's tests (where there were at least 10 studies). The authors provided method details for investigating the iron dose-response relation with risk of maternal anaemia, low birth weight and preterm birth.

Results of the review
Fourty-eight randomised trials (17,793 women) and 44 cohort studies (1,851,682 women) were included. Eighteen randomised trials were classed as high quality.

Compared with controls, iron use (with or without folic acid) increased maternal mean haemoglobin (WMD 4.59 g/L, 95% CI 3.72 to 5.46; $I^2=0%$; 36 trials) and significantly reduced the risk of anaemia in the third trimester or at delivery (RR 0.50, 95% CI 0.42 to 0.59; $I^2=83%$; 19 trials; a funnel plot suggested the presence of publication bias), iron deficiency (RR 0.59, 95% CI 0.44 to 0.79; $I^2=79%$; eight trials), iron deficiency anaemia (RR 0.40, 95% CI 0.26 to 0.60; $I^2=33%$; six trials) and low birth weight (RR 0.81, 95% CI 0.71 to 0.93; $I^2=1%$; 13 trials). The effect of iron on preterm birth was not significant.

Analysis of cohort studies showed a significantly higher risk of low birth weight (adjusted OR 1.29, 95% CI 1.09 to 1.53; $I^2=90%$; six studies) and preterm birth (adjusted OR 1.21, 95% CI 1.13 to 1.30; $I^2=0%$; seven studies) with anaemia in the first or second trimester. Exposure-response analysis indicated that for every 10 mg increase in iron dose/day up to 66 mg/day, the relative risk of maternal anaemia was 0.88 (95% CI 0.84 to 0.92). Birth weight increased (WMD 15.1 g, 95% CI 6.0 to 24.2; 18 trials) and risk of low birth weight decreased by 3% (RR 0.97, 95% CI 0.95 to 0.98; 13 trials) for every 10 mg increase in dose/day. The linear trend was considered to be statistically significant. For each 1 g/L increase in mean haemoglobin, birth weight increased by 14.0 g (95% CI 6.8 to 21.8; 16 trials). No evidence of a significant effect was noted for duration of gestation, small for gestational age births and birth length.

Further results were reported.

Authors' conclusions
Daily prenatal use of iron substantially improved birth weight in a linear dose-response fashion, probably leading to a reduction in risk of low birth weight. An improvement in prenatal mean haemoglobin concentration linearly increased birth weight.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria. Attempts to identify relevant studies in any language were undertaken by searching electronic databases and checking references. Five studies available only as abstracts and 11 studies that could not be translated were excluded; this was unlikely to have had much impact on most of the review results because of the large number of studies included in the review. Suitable methods (such as independent duplicate processes) were used to reduce the risk of reviewer error and bias throughout the review.

Study quality was assessed and the results were used to inform sensitivity analyses. The authors classed some trials as being high quality despite either unclear/inadequate blinding or losses to follow-up; full details for studies were not presented so the possibility of bias in some high quality studies could not be ruled out. Other individual study details were provided in full and appropriate methods were used to pool data and to assess and investigate heterogeneity. Not all heterogeneity could be explained.

The authors' conclusions are likely to be reliable.

Implications of the review for practice and research

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Practice: The authors stated that the use of iron in women during pregnancy may be used as a preventive strategy to improve maternal haematological status and birth weight. They added that targeted interventions to strengthen the infrastructure of antenatal care should be used in high-burden countries.

Research: The authors stated that future research was needed to explore feasible strategies of iron delivery in a country setting and to evaluate the effectiveness of other strategies, such as fortification and dietary diversification.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.