REVIEW Open Access

Abstract

Introduction:

Methods:

are disproportionately affected by iron deficiency, and it is this group that stands to gain the most by its reduction.

Anemia, as defined by low hemoglobin or hematocrit, is commonly used to assess the severity of iron deficiency in populations without high rates of malaria. The high physiological requirement for iron in pregnancy is difficult to meet with most diets. Therefore, pregnant women should routinely receive iron supplementation, especially in developing countries. Prenatal iron supplementation is not compulsory in many industrialized countries and the recommended dose is usually small (30 mg ferrous iron daily) [6]. However, for developing countries, the recommendation is a daily dose of 60 mg of iron for pregnant, non-anemic women for six months and an increased dose of 120 mg of iron daily if the duration of supplementation is shorter, if iron deficiency prevalence in women of a given country is high, and if pregnant women are anemic. This supplement should include 400 μg of folic acid or lower doses if this amount is not available [7].

Earlier studies have provided sufficient evidence to show that iron supplementation with or without folic acid results in a significant reduction in the incidence of anemia during pregnancy [2,8]. There has also been a limited impact of iron supplementation in community settings owing to lack of compliance and poor infrastructure [9]. However, data regarding quality of evidence for the effectiveness of iron during pregnancy are lacking. Besides, the data on studies in developing countries have not been presented separately. This article is one of the series of papers that aim to determine efficacy of interventions for recommendations into the Lives Saved Tool (LiST), especially in developing countries and is, therefore, different from previously published systematic reviews. In LiST, increases in coverage of an intervention results in a reduction of risk factor or one or more causes of mortality. In this review, the recommendations are made based on application of adapted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for the quality of evidence and use of the Child Health Epidemiology Reference Group (CHERG) rules. For more details of the review methods, the adapted GRADE approach or the LiST model, see the methods paper for by CHERG group [10].

Methods

Searching

We systematically reviewed all published literature up to June 21, 2010 to identify studies of iron supplementation with or without folic acid during pregnancy on maternal anemia. As per the Child Health Epidemiology Reference Group (CHERG) systematic review guidelines [10], we searched PubMed and the Cochrane Library, and included publications in any language available in these databases. Every effort was made to gather unpublished data when reports were available for full abstraction. Previous reviews on the topic were also hand-searched to look for relevant studies [2,8,11]. We used the Medical Subject Heading Terms (MeSH) and free text terms for the search strategy using a combination of terms for iron, folic acid and pregnancy, as follows:

("Iron"[Mesh OR "Folic Acid"[Mesh] OR iron OR folic acid OR folate) AND ("Anemia"[Mesh] OR "Anemia, Iron-Deficiency"[Mesh] OR anemia) AND (pregnancy OR maternal)

Inclusion/exclusion criteria

We limited our search to randomized and quasi-randomized trials conducted in both developed and developing countries, comparing the effects of preventive prenatal oral iron or iron + folic acid supplements among pregnant women versus no treatment/placebo. The developing countries were defined as countries with Gross National Income per capita (GNI) below US $11,905, according to World Bank [12]. Pregnant mothers could be of any age or parity. Studies were included if iron or iron-folate was given alone to the intervention group. Those studies were excluded that assessed the effects of multiple combinations of vitamins and minerals except even if iron/iron-folate was the only difference among the study groups (arms). All included studies contained a placebo or a suitable control group that did not contain iron or iron-folate. There were no limits on gestational age at the time of enrolment in the study and the duration of supplementation. Studies of peri-conceptional or postpartum iron/iron-folate supplementation were excluded. Studies of fortification of iron/iron-folate in food or studies in

nausea, vomiting, headache or constipation among the pregnant mothers.

Abstraction, analyses and summary measures

Studies were included if data from one of the following outcomes was provided: anemia at term, iron deficiency anemia at term, severe anemia at term and severe anemia at any time during the second and third trimester. All outcome measures to be included were determined a priori. The interventions described in this review can be subdivided into four categories: 1) daily iron supplementation alone compared to placebo/control, 2) weekly iron supplementation alone compared to daily regimen, 3) daily supplementation of iron and folic acid versus placebo/control and 4) weekly supplementation of iron and folic acid versus daily supplementation.

All studies that met final inclusion and exclusion criteria were double-data abstracted into a standardized form for each outcome of interest. We abstracted key variables with regard to the study identifiers and context, study design and limitations, intervention specifics, and outcome effects. Each study was assessed and graded according to the CHERG adaptation of the GRADE technique [15]. Studies received an initial score of high if they were RCTs or cluster-RCTs (cRCTs). The grade was decreased by 0.5 - 1 point for each study design limitation like inadequate methods of sequence generation, allocation concealment and attrition > 20% etc. In addition, studies reporting an intent-to-treat analysis or with statistically significant strong levels of association (> 80% reduction) received 0.5 – 1.0 grade increase. Any study with a final grade of very low was excluded on the basis of inadequate study quality.

For any outcome with more than one study, we conducted a meta-analysis and reported the Mantel-Haenszel pooled relative risk and corresponding 95% confidence interval (CI). In case of heterogeneity ($P < 0.1$ and $I^2 > 50\%$), the random effect model (DerSimonian-Laird) pooled relative risk and corresponding 95% CI was used, especially where there was unexplained heterogeneity such as major differences in study design [10]. All analyses were conducted using RevMan 5 statistical software.

We summarized the evidence based on outcome by including assessment of the study quality and quantitative measures according to standard guidelines [10] for each outcome. For the outcomes of interest, namely the effect of iron/iron-folate on maternal anemia, we applied the CHERG Rules for Evidence Review [10] to recommend final estimates for reduction in anemia with iron or iron-folate supplementation. Additional file 1 contains a list of studies from the search that were excluded from the meta-analyses with a brief explanation for why the study was excluded.

Definitions

Anemia was defined as hemoglobin (Hb) level of less than 110g/L and severe anemia was defined as hemoglobin level of less than 70g/L. Iron deficiency anemia was defined as Hb less than 110 g/L and at least one additional laboratory indicator (mean cell volume, haemo-

versus no intervention/placebo, as seen in 8 studies [18,23,27,30,33,34,41,45], had a non significant adverse impact on severe anemia at term (RR = 4.83; 95% CI: 0.23 - 99.88; random model). This result was primarily based on one study [33] as all the other studies had zero events in both groups. Three studies evaluated the impact of daily supplementation with iron and folate both on severe anemia at term [16,18,31], but the num-

Table 1 Quality assessment of trials of iron and/or folate on the incidence of anemia during pregnancy

	Quality Assessment					Summary of Findings		
No of studies (ref)	Design	Limitations	Consistency	Directness		No of events		
				Generalizability to population of interest	Generalizability to intervention of interest	Intervention	Control	Relative Risk (95% CI)
Daily iron versus no intervention/placebo ***Anemia at term: Moderate outcome specific qualit***								
14	/	a				114	313	(a) 0.2 0.1 , 0.42
Daily iron versus no intervention/placebo***: Iron deficienc anemia at term: Moderate outcome specific qualit***								
	/	a				2		(a) 0.33 0.1 , 0.
Daily iron and folic acid versus no intervention/placebo***: Anemia at term: Moderate outcome specific qualit***								
3	/	a				1	4	(a) 0.2 0.12, 0.
Daily iron and folic acid versus no intervention/placebo: ***Iron deficienc anemia at term: Lo outcome specific qualit***								
1	a	a	a			12		(a) 0.43 0.1 , 1.0

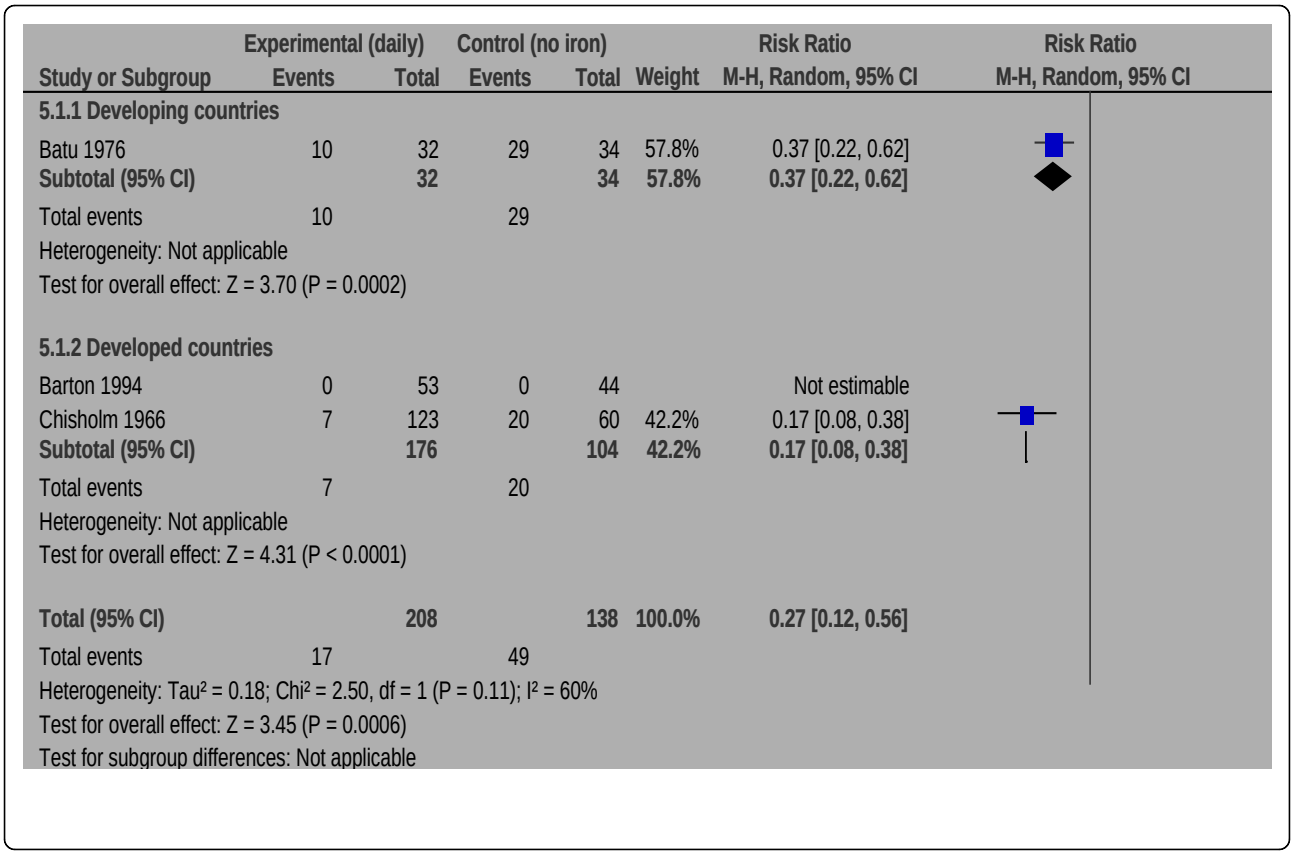
anemia and iron deficiency anemia at term with daily iron supplementation and that of anemia at term due to daily iron-folate supplementation versus no intervention/placebo.

The pooled analysis of effect of daily iron supplementation vs. control had a high heterogeneity (fig 2). The most likely explanation of this substantial statistical heterogeneity (I^2 =73 %) is the variable effect size of the studies which in turn depend on the baseline anemia status of the study population. An important observation to make is that the direction effect in all the studies was in the same direction. We can expect that biologic effect of iron supplementation would differ based on prevalence of anemia in the study population. To further elaborate on this observation, we conducted a post hoc subgroup analysis based on baseline anemia status of the study population (data not shown). There were seven studies that included only non-anemic pregnant women based on laboratory evidence of absence of anemia (hemoglobin < 110 g/L) [21,23,24,27,29,33,39] and in other seven studies, population was that of mixed status [17,19,30,34,37,38,41]. Pooled estimates for non-anemic women were less heterogeneous (I^2 =47%) and size of summary estimate was less prominent (RR 0.31, 95 % CI 0.19-0.52) compared to that of mixed population that had more heterogeneous (I^2=83%) and more prominent results (RR 0.22, 95 % CI 0.11-0.47). This shows a strong biologic effect in favor of the intervention and also indicates that effect of Iron supplementation would depend on degree of baseline anemia in the study population.

CHERG rules were applied to the collective outcomes of anemia for recommendation of iron deficiency anemia into the LiST model. Daily supplementation with iron led to 73% reduction in incidence of anemia at term as compared to no supplementation. This intervention had a 'moderate' quality evidence owing to some limitations in included studies like unclear [17,21,24,30,34,38,39,41] or inadequate sequence generation [19], and high loss to follow up [17,23,27]. Another limitation was that all the studies in the pooled analysis were not conducted in developing countries. In any case, based on strong biologic plausibility and consistent direction of effect across the studies, we recommend a 73 % reduction in anemia at term with iron supplementation during pregnancy, for inclusion in the LiST model. Daily supplementation with iron and folate led to 73% reduction in incidence of anemia at term when

compared with no supplementation. We recommend this estimate for reduction in anemia at term for inclusion in the LiST model. The quality of evidence regarding this intervention had to be down-graded from 'high' to moderate due to some limitations like high loss to follow up [17] and unclear sequence generation [21] and also the fact that all the studies were not conducted in developing countries.

Our results show that there was not much difference in effect between iron alone and iron-folate combined. The effect sizes were similar for both the analyses but CIs were wider for that of iron/folate, mainly due to less number of studies in the pooled analysis. This shows that we can expect a similar biological effect when the iron is supplemented alone or in combination with folate. We did a subgroup for developing and developed


Experimental (daily)
Control (no iron)
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
5.1.1 Developing countries
Batu 1976 10 32 29 34 57.8% 0.37 [0.22, 0.62]
Subtotal (95% CI) 32 34 57.8% 0.37 [0.22, 0.62]
Total events 10 29
Heterogeneity: Not applicable
Test for overall effect: Z = 3.70 (P = 0.0002)
5.1.2 Developed countries
Barton 1994 0 53 0 44 Not estimable
Chisholm 1966 7 123 20 60 42.2% 0.17 [0.08, 0.38]
Subtotal (95% CI) 176 104 42.2% 0.17 [0.08, 0.38]
Total events 7 20
Heterogeneity: Not applicable
Test for overall effect: Z = 4.31 (P < 0.0001)
Total (95% CI) 208 138 100.0% 0.27 [0.12, 0.56]
Total events 17 49
Heterogeneity: Tau² = 0.18; Chi² = 2.50, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 3.45 (P = 0.0006)
Test for subgroup differences: Not applicable

Southeast Asia, West Pacific and Africa [48]. This shows that amount of effect would be substantially high in developing countries however more efficacy trials are required to determine the conduct of the intervention.

Weekly iron and folic acid supplementation (WIFS) is a relatively new phenomenon, and there is very little data at the moment comparing weekly supplementation with daily dosage. Weekly iron and folic acid supplementation, in synchrony with the turnover of mucosal cells, may be a promising substitute for daily iron sup-

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34. . *Dan Med Bull* 1 1, **38(6)**/4 1-4 .

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