Impact of multiple micronutrient versus iron–folic acid supplements on maternal anemia and micronutrient status in pregnancy

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Abstract

Background. Multiple micronutrient supplements could increase hemoglobin and improve micronutrient status of pregnant women more than iron supplements alone or iron with folic acid.

Objective. To compare the effects of multiple micronutrients with those of iron supplements alone or iron with folic acid, on hemoglobin and micronutrient status of pregnant women.

Methods. Studies were identified in which pregnant women were randomized to treatment with multiple micronutrients, or with iron with or without folic acid. A pooled analysis was conducted to compare the effects of these supplements on maternal hemoglobin, anemia, and micronutrient status. Effect size was calculated for individual and combined studies, based on mean change from baseline to final measure in the group receiving iron, with or without folic acid, minus the mean change in the group, divided by the pooled standard deviation of the two groups. The effect on the relative risk of anemia or iron deficiency was calculated as the probability of anemia or iron deficiency in the group receiving multiple micronutrients divided by the probability in the group receiving iron, with or without folic acid.

Results. Multiple micronutrient supplements had the same impact on hemoglobin and iron status indicators as iron with or without folic acid. There was no overall effect on serum retinol or zinc. In the only study in which status of other micronutrients was analyzed, a high prevalence of multiple deficiencies persisted in the group receiving multiple micronutrients provided with daily recommended intakes of each nutrient.

Conclusions. Multiple micronutrient supplements increased hemoglobin synthesis to the same extent as supplementation with iron with or without folic acid, although often they contained lower amounts of iron. The amount of supplemental iron and other nutrients that can enable pregnant women with micronutrient deficiencies to achieve adequate status remains to be determined.

Key words: Folic acid, iron, multiple micronutrients, pregnancy, supplements

Introduction

Maternal consumption of multiple micronutrient supplements during pregnancy should improve indicators of maternal micronutrient status more than the iron supplements, with or without folic acid, more commonly provided, but there has been no previous review of the extent to which supplements providing close to the daily recommended intake of multiple micronutrients affect nutritional status indicators. Multiple micronutrient supplements should help to reduce anemia, because other nutrients that are often lacking in the diets of pregnant women in poor populations, including vitamin A, riboflavin, and vitamins B_6 and B_12, are also needed for hemoglobin synthesis. Improving maternal status of other micronutrients could also benefit pregnancy outcome, infant micronutrient stores...
at birth, and breast milk content of the nutrients [1].

The purpose of the present analysis is to determine whether multiple micronutrient supplements have greater effects on anemia and micronutrient status during pregnancy than do supplements of iron, with or without folic acid.

**Methods**

Data on micronutrient status were obtained, when available, from the United Nations International Multiple Micronutrient Preparation (UNIMMAP) supplementation studies. However, this article differs from the other meta-analyses reported in this Supplement because of the inclusion of several studies that specifically examined micronutrient outcomes; few of the UNIMMAP studies had much data on micronutrient status. The sources of available data on hemoglobin and indicators of iron and vitamin A status and micronutrient contents of the supplements are shown in table 1 [2–16]. In most of the studies, the multiple micronutrient supplement contained at least 11 or 12 micronutrients, although in some only 1 or 2 micronutrients were added to the iron and folic acid. In 5 (UNIMMAP studies) of the 13 studies analyzed here, there was twice as much iron (60 mg) in the supplement containing iron, with or without folic acid, as in the multiple micronutrient supplement (30 mg). Because a relatively small amount of data was available on other nutritional status indicators, the sources of this information are referred to in the relevant sections of the text.

Effect sizes were calculated as the mean of the control group (i.e., supplemented with iron, with or without folic acid) minus the mean of the group receiving multiple micronutrients divided by the pooled standard deviation of the two groups. When available, the effect size was based on the changes from baseline to final measurement and the standard deviations of the changes. When this information was unavailable, the effect size was calculated from the mean and standard deviation of the final value. Confidence intervals were calculated for each effect size; intervals that do not include 1.0 are statistically significant. An effect size of 0.2 was considered small, 0.5 moderate, and 0.7 large.

For anemia and iron-deficiency anemia, the effect of multiple micronutrients compared with that of iron, with or without folic acid, on the relative risk of these conditions was calculated as the probability of anemia or iron deficiency in the group receiving multiple micronutrients divided by the probability of anemia or iron deficiency in the group receiving iron, with or without folic acid.

**Results**

**Anemia and iron status**

All studies, including all the UNIMMAP trials, had data on hemoglobin, except for one that recorded hematocrit [9]. Among the individual trials, the only statistically significant effect sizes were found in Mexico (a negative effect, with a smaller change in hemoglobin during pregnancy in the group receiving multiple micronutrients than in the iron group) and in Nigeria and Tanzania (positive effects) (fig. 1). Overall, as indicated on the right of figure 1, multiple micronutrients did not increase hemoglobin more than iron, with or without folic acid, alone. The same was true of iron status, with the multiple micronutrients

![FIG. 1. Effect sizes for hemoglobin or hematocrit in the groups receiving multiple micronutrients vs. the groups receiving iron, with or without folic acid. Guinea-Bissau = ref. 2, 1 = 1 RDA, 2 = 2 RDA; Indonesia I = ref. 3, M = ref. 4, S = ref. 5; Nepal C = ref. 7 and Nepal O = ref. 8; Peru O = ref. 11 and Peru Z = ref. 12.](image)

![FIG. 2. Effect sizes for serum ferritin in the groups receiving multiple micronutrients vs. the groups receiving iron, with or without folic acid](image)
### TABLE 1. Sources of data on indicators of iron and vitamin A status

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Multiple micronutrients</th>
<th>Hemo-globin</th>
<th>Ferritin</th>
<th>Anemia</th>
<th>Iron-deficiency anemia</th>
<th>Serum transferrin receptor</th>
<th>Retinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea-Bissau [2]</td>
<td>Iron 60 mg</td>
<td>Iron 30 mg</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Folic acid 400 µg</td>
<td>14 micronutrients UNIMMAP</td>
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<tr>
<td>Guinea-Bissau [2]</td>
<td>Iron 60 mg</td>
<td>Iron 30 mg</td>
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<td></td>
<td>Folic acid 400 µg</td>
<td>2 RDA of 14 micronutrients UNIMMAP</td>
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<tr>
<td>Indonesia [3]</td>
<td>Iron 60 mg</td>
<td>Iron 30 mg</td>
<td>√</td>
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<tr>
<td></td>
<td>Folic acid 400 µg</td>
<td>14 micronutrients UNIMMAP</td>
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<tr>
<td>Indonesia [4]</td>
<td>Iron 120 mg weekly</td>
<td>Iron 120 mg weekly Folic acid Vitamin A</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Indonesia [5]</td>
<td>Iron 50 mg</td>
<td>Iron 50 mg Vitamin A Vitamin B&lt;sub&gt;2&lt;/sub&gt; Folic acid UNIMMAP</td>
<td>√</td>
<td></td>
<td></td>
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<tr>
<td>Mexico [6]</td>
<td>Iron 60 mg</td>
<td>Iron 62 mg 12 micronutrients</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Nepal [7]</td>
<td>Iron 60 mg</td>
<td>Iron 60 mg</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Nepal [8]</td>
<td>Iron 60 mg</td>
<td>Iron 30 mg UNIMMAP</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Nigeria [9]</td>
<td>Iron 50 mg</td>
<td>Iron 50 mg</td>
<td>√</td>
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<tr>
<td>Pakistan [10]</td>
<td>Iron 60 mg</td>
<td>Iron 30 mg UNIMMAP</td>
<td>√</td>
<td>√</td>
<td></td>
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<tr>
<td>Peru [11, 12, 13]</td>
<td>Iron 60 mg</td>
<td>Iron 60 mg Folic acid Zinc</td>
<td>√</td>
<td>√</td>
<td></td>
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<td></td>
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<tr>
<td>Tanzania [14]</td>
<td>Iron 60 mg through health center Placebo</td>
<td>Iron 10 mg 10 micronutrients Iron 60 mg through health center</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
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<tr>
<td>Indonesia [15]</td>
<td>Iron 30 mg</td>
<td>Iron 30 mg Folic acid β-carotene Zinc</td>
<td>√</td>
<td>√</td>
<td></td>
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<td></td>
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<tr>
<td>Zimbabwe [16]</td>
<td>Iron Folic acid through health system</td>
<td>13 micronutrients Iron Folic acid through health system</td>
<td>√</td>
<td>√</td>
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</tbody>
</table>

a. The United Nations International Multiple Micronutrient Preparation (UNIMMAP) supplement contains 30 mg of iron, 15 mg of zinc, 2 mg of copper, 65 µg of selenium, 150 µg of iodine, 800 µg RE of vitamin A, 1.4 mg of vitamin B<sub>1</sub>, 1.4 mg of vitamin B<sub>2</sub>, 400 µg of folic acid, 18 mg of niacin, 1.9 mg of vitamin B<sub>6</sub>, 2.6 µg of vitamin B<sub>12</sub>, 70 mg of vitamin C, 200 IU of vitamin D, and 10 mg of vitamin E.

b. Measured by hematocrit.
failing to increase serum ferritin more than iron, with or without folic acid, in any study or overall (fig. 2). Transferrin receptors were measured in only three locations. In Nepal [7], there was no significant difference in the change in concentration between the group that received iron plus folic acid plus vitamin A and the group that received multiple micronutrients, but both groups had lower concentrations (better iron status) at the end of the study than groups that received folic acid plus vitamin A alone, with no iron. Similarly, the change in transferrin receptor concentrations was the same in pregnant women given iron, with or without folic acid, plus vitamin A as in those given iron, with or without folic acid, alone [4]. In Peruvian pregnant women, the final mean serum transferrin receptor concentrations did not differ between a group receiving iron, with or without folic acid, and a group receiving iron, with or without folic acid, plus zinc, and both of these groups had significantly lower final concentrations than a control group that did not receive iron [11].

The relative risk of anemia could be compared in four studies [4, 7, 8, 13] and was not different in the group receiving multiple micronutrients or overall, from that in the groups receiving iron, with or without folic acid. The risk of iron-deficiency anemia could be compared only in Mexico [6], Nepal [7], and Tanzania [13]. In none of these trials was the risk different by supplement group.

Information is almost completely lacking on the effect of maternal multiple micronutrient supplementation in pregnancy on infant hemoglobin or iron status. In the only three studies that measured hemoglobin, hematocrit, or serum ferritin in cord blood, there was no difference between the multiple micronutrient and the iron–folic acid groups [9, 11, 12].

**Vitamin A and other micronutrients**

Of the eight trials that had data on serum retinol concentrations, one found a significant positive effect of the multiple micronutrient supplement [3] and one a significant negative effect [4], but there was no effect overall for the trials combined (fig. 3). There was significant heterogeneity of the serum retinol response to multiple micronutrients among the trials, perhaps not surprisingly, since the dose varied across studies.

Changes in serum zinc were measured in only three studies. Adding zinc to iron supplements, with or without folic acid, increased maternal serum zinc concentrations in Peru [13], although the same group observed that women supplemented with iron plus folic acid, or iron plus folic acid plus zinc, had lower serum zinc concentrations than a group that had no prenatal supplements [11]. The two other studies found no difference in serum zinc concentrations of pregnant women when zinc was provided compared with iron alone, with or without folic acid [4, 16].

The most thorough examination of maternal micronutrient status was conducted in one study in Nepal [17]. The supplements (400 µg of folic acid; 400 µg of folic acid plus 60 mg of iron; 400 µg of folic acid plus 60 mg of iron plus 30 mg of zinc; or multiple micronutrients containing the same amounts of folic acid, iron, and zinc plus 11 other micronutrients) were provided prior to conception, and final measures of maternal status were obtained at 32.6 weeks of pregnancy. Serum folate was significantly increased in all of the groups receiving supplements in comparison with the control group receiving vitamin A alone. However, only the multiple micronutrient supplement increased serum vitamin B₁₂, riboflavin, vitamin B₆, 25-hydroxyvitamin D, and zinc compared with the values in the control group. In spite of these overall significant improvements in micronutrient status, a high proportion of the women were still deficient in all nutrients (except vitamin A) in the third trimester, especially vitamin B₁₂ (65% of women), vitamin B₆ (66%), riboflavin (37%), and zinc (87%). This raises the question of whether the micronutrient content of the supplements, which contained approximately the recommended daily intake of each nutrient and were taken daily from early pregnancy, was high enough. Subclinical infections may also have affected the micronutrient status markers [17, 18].

**Discussion**

Comparisons among the studies reviewed in this analysis should be made with caution, because of differences in the composition of micronutrient supplements, the frequency and duration of supplementation, and initial rates of anemia and iron deficiency. However, some general conclusions can be drawn. Most of the studies limited their assessment of nutritional status to
measures of hemoglobin and iron status. Overall, the multiple micronutrients produced the same effect as iron, with or without folic acid, on hemoglobin concentrations, anemia, and iron status, although many of the multiple micronutrient supplements contained lower amounts of iron. When maternal iron supplementation is started relatively early in pregnancy (i.e., during the second trimester at the latest), it is unlikely that 60 mg of iron will be more effective for improving hemoglobin or iron status than 30 mg [19, 20]. The analysis also indicates that adding the other micronutrients did not impair the efficacy of the iron supplements.

The amount of vitamin A contained in the supplements did not increase serum retinol concentrations. This was perhaps because of insufficient fat in the diet to enable absorption, inadequate amounts of vitamin A in the supplement, or poor sensitivity of serum retinol as the indicator.

Only one study, conducted in rural Nepal, measured more than a few nutritional status indicators [17]. This study revealed that a high prevalence of multiple micronutrient deficiencies persisted in late pregnancy, even though the multiple micronutrient supplement was provided throughout gestation. Although rural Nepal may have a greater micronutrient deficiency problem than many developing countries, these results do illustrate the need to include other micronutrients in supplements for such populations, and raise the possibility that the doses used—typically around the recommended intake for pregnant women—were not sufficient to restore nutritional status to normal. In this regard, it is noteworthy that other studies have safely provided substantially higher quantities of some micronutrients in multiple micronutrient supplements for pregnant women [2, 18]. More work is needed to determine the dose of each specific micronutrient that is sufficient to improve, and ideally restore, maternal nutritional status during pregnancy, without producing any adverse effects. This has never been studied systematically but could be feasible to study in smaller groups of women than in the larger pregnancy outcome trials, if nutritional status is studied as the outcome of interest rather than measures such as birthweight. If possible, samples from the Guinea-Bissau trial [2] should be analyzed for indicators of multiple micronutrient status, as the multiple micronutrient supplement in that trial was given both at the recommended daily allowance level and at twice that dose (except for iron).

Conclusions

The effects of multiple micronutrients on maternal hemoglobin, hematocrit, and iron status did not differ from the effects of iron alone, with or without folic acid. There was no significant effect of the multiple micronutrients on serum retinol or zinc. The persistence of deficiency of many nutrients indicates that at present there is inadequate information from which to develop the most effective multiple micronutrient supplements for pregnant women consuming poor-quality diets, although it is unlikely that one formulation will be ideal for all. Attention to this question should take priority, as it is doubtful that providing iron and folic acid alone will be adequate to meet the needs of most of these women during pregnancy.

Acknowledgments

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References

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