Multivitamin-mineral supplementation is not as efficacious as is iron supplementation in improving hemoglobin concentrations in nonpregnant anemic women living in Mexico[1–4]

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ABSTRACT

Background: Iron supplements improve hemoglobin status and reduce anemia due to iron deficiency. It is not known whether multiple micronutrient (MM) supplements are as efficacious as are iron supplements alone in improving hemoglobin concentrations.

Objective: We conducted a randomized, double-blind community trial in Mexico to compare the efficacy of MM supplements containing iron with that of iron alone in improving hemoglobin concentrations in nonpregnant women.

Design: Nonpregnant women (n = 158) were recruited from a semirural community in Mexico and were randomly assigned to receive iron alone (60 mg; Fe group) or MM supplements (vitamins A, B complex, C, D, E, and K and iron, zinc, and magnesium; MM group) 6 d/wk in their home for 12 wk. Hemoglobin concentrations were measured in capillary blood samples at baseline and follow-up.

Results: The treatment groups (MM: n = 75; Fe: n = 77) did not differ significantly at recruitment in age, schooling, literacy, or socioeconomic status. There were no significant differences between groups in compliance (median: 97.5%), baseline hemoglobin concentrations, or prevalence of anemia (20%). Losses to follow-up (4%) and mean (±SD) changes in hemoglobin (MM group: 6.7 ± 10.6 g/L; Fe group: 7.1 ± 13.6 g/L) were not significantly different between groups. However, the change in hemoglobin in anemic subjects was greater in the Fe group than in the MM group ($P < 0.05$ for interaction), and there was no significant difference in nonanemic subjects.

Conclusions: MM supplements may not be as efficacious as is iron alone in improving the hemoglobin status of anemic women. *Am J Clin Nutr* 2004;80:1308–11.

KEY WORDS Iron, multivitamin-mineral supplements, hemoglobin, anemia, nonpregnant women

INTRODUCTION

Anemia is a major public health problem worldwide and is associated with serious physiologic consequences that include impairment of cardiovascular performance, reduced work productivity, higher incidence of low birth weight and premature delivery, and increased maternal mortality (1–3). Anemia, defined as a condition caused by a decrease in red blood cells or hemoglobin in the blood (3–5), is primarily caused by iron deficiency—the most common nutrient deficiency in the world. It is estimated that 40% of the world's population (2 billion people) is anemic, of which ≈50–75% is due to iron deficiency (3). Although iron supplements are efficacious in improving iron status and reducing anemia (6), recent evidence suggests that under programmatic conditions, little improvement has been made in reducing the prevalence of anemia in vulnerable groups, such as young children and women of reproductive age (7). This has led to questions about the bioavailability of iron and the contribution of other nutrient deficiencies in the development and progression of anemia. The bioavailability of iron is partially dependent on what other components are ingested with the iron. For example, vitamin C aids in the absorption of iron, whereas zinc and copper may inhibit absorption (8). Besides iron, other micronutrient deficiencies can also lead to anemia. Folate and vitamin B-12 also play causal roles in the development of anemia because of their integral function in nucleotide synthesis and red blood cell development. Vitamin A has also been shown to play a role in the etiology and treatment of anemia (9). Controlled trials have shown that vitamin A works in conjunction with iron to elevate hemoglobin concentrations in anemic children and women (10, 11).

As in other developing countries, diets in Mexico are often deficient in various micronutrients such as iron, zinc, vitamin A, and vitamin B-12 (12). This is primarily due to the ingestion of foods that are not of animal origin and that are high in phytates, which are inhibitors of iron absorption. There has been considerable interest in strategies that would improve the intakes of several nutrients simultaneously (13). Although recent studies have examined the role of multiple micronutrient (MM) supplements in improving pregnancy outcomes and child growth, little is known about the positive or negative effects of MM supplements in improving hemoglobin concentrations in anemic and

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TABLE 1
Composition of the multiple micronutrient supplement[1]

Nutrient	Amount	Percentage of RDA[2]
		%
Vitamin A (IU)	2150	92
Vitamin D_3 (IU)	309	155
Vitamin E (IU)	5.73	26
Thiamine (mg)	0.93	85
Riboflavin (mg)	1.87	170
Niacin (mg)	15.5	111
Folic acid (μg)	215	54
Vitamin B-6 (mg)	1.94	150
Vitamin B-12 (μg)	2.04	85
Vitamin C (mg)	66.5	89
Zinc (mg)	12.9	161
Iron (mg)	62.4	347
Magnesium (mg)	252	79

[1] Both the intervention and control groups received 60 mg Fe in the form of ferrous sulfate and were supplemented for 6 d/wk for 12 wk.

[2] Based on the recommended dietary allowance (RDA) for nonpregnant women of reproductive age (15).

nonanemic women. We therefore conducted a randomized, double-blind controlled trial to evaluate the efficacy of an MM supplement containing iron compared with that of iron supplementation alone on the effect of iron in improving hemoglobin concentrations in nonpregnant women of reproductive age.

SUBJECTS AND METHODS

A randomized, double-blind controlled trial was conducted in a semirural community outside of Cuernavaca, Morelos, Mexico, between June and October 2002. The supplements used in this study had been originally formulated for use in an intervention trial for pregnant women (14). The actual composition of the MM supplement and the percentage recommended dietary allowance (RDA) met for nonpregnant women are shown in **Table 1** (15). Both supplements contained 60 mg Fe in the form of ferrous sulfate. This study was a collaborative effort between the Department of International Health at Emory University in Atlanta and the Centro de Investigación en Nutrición y Salud at the Instituto Nacional de Salud Pública located in Cuernavaca, Morelos, Mexico.

Through home visitation, after a detailed explanation of the study procedures, risks and benefits, trained fieldworkers invited nonpregnant women of childbearing age to participate. All eligible women willing to sign an informed consent form were randomly assigned to 1 of 2 treatment groups: iron alone (60 mg; Fe group) or MM supplements (vitamins A, B complex, C, D, E, and K and iron, zinc, and magnesium; MM group) 6 d/wk in their home for 12 wk with the use of a computer-generated list and color coding to ensure blinding. Women who were pregnant or suspected that they might have been (last menstrual period >6 wk previously) were excluded. Women with severe anemia (hemoglobin ≤ 70 g/L) were also excluded from the study; these women were provided with iron supplements and referred to the study doctor. No other women were excluded and, thus, the sample included both anemic and nonanemic subjects. The institutional review boards of the Emory University and Instituto Nacional de Salud Pública approved the study protocol.

At baseline, a trained technician took a capillary blood sample from a finger prick and measured hemoglobin concentrations with a portable photometer (Hemocue) at the study headquarters. Socioeconomic status (SES) was also assessed at the same time by a trained fieldworker using a questionnaire that had been used in previous studies and included questions about household size, occupation, education, water and sanitation, and ownership of household goods. Indigenous ethnicity in this population was defined on the basis of the ability to speak or understand an indigenous language (Nahuatl) as well as Spanish. This definition is commonly used in Mexico for health and demographic surveys. Trained fieldworkers administered and recorded the consumption of supplements during household visits 6 d/wk. The supplements were distributed during the course of the day and were usually consumed by participants between meals. Compliance, measured as the percentage of total tablets offered that were consumed, was based on the direct observation of ingestion of supplements. At the end of 12 wk, the participants returned to the study headquarters, where hemoglobin concentrations were measured by using methods similar to those used at baseline.

The effectiveness of randomization was assessed for baseline characteristics by using a Student's *t* test for normally distributed variables and a chi-square test of proportions for categorical variables. An index of economic status was created by using factor analysis and included variables such as type of house materials (walls, floor, and roof) and employment. The main outcome variable was hemoglobin concentration. Anemia was defined by using the WHO definition, ie, a hemoglobin concentration <120 g/L (16), without adjustment for altitude (the community is located <1000 m above sea level). The mean change in hemoglobin (baseline to follow-up) was compared between treatment groups by using a two-sample *t* test. A P value < 0.05 was considered statistically significant. Effect modification by baseline hemoglobin, age, and SES status was also evaluated by testing for interactions with treatment group in multiple linear regression analysis and were considered statistically significant at $P < 0.10$. SAS version 8.2 was used for all data analysis.

RESULTS

Of the 158 women assigned to treatment, 152 completed the 12 wk of supplementation. No women were excluded for severe anemia or pregnancy. Of the 6 women lost to follow-up, 3 were from each treatment group, and the reasons did not differ between groups. There were no differences in age, years of schooling, literacy, indigenous ethnicity, and SES by treatment group (**Table 2**). The mean age of the women was 28.6 ± 7.8 y, and most were literate. Compliance was high (median: 97.5%) and did not differ by treatment groups. Mean hemoglobin concentrations were not significantly different between the 2 treatment groups at baseline or at the end of the study (**Table 3**). The prevalence of anemia did not differ between treatment groups at baseline (MM group: 21%; Fe group: 19%; $P = 0.78$). The prevalence of anemia declined by almost one-half in both groups, but there were no significant differences by treatment group (12% and 9% in the MM and Fe groups, respectively; $P = 0.56$). On the basis of the multiple regression results for subjects who were anemic at baseline, the mean change in hemoglobin was higher in the Fe group than in the MM group (**Figure 1**); no significant difference was observed in nonanemic subjects ($P < 0.05$ for interaction). There was no evidence of effect modification by age or SES.

TABLE 2
Baseline demographic and socioeconomic characteristics of the 2 supplementation groups[1]

	MM group (n = 75)	Fe group (n = 77)	P
Age (y)	28 ± 7.5[2]	30 ± 8.2	0.13
Duration of schooling (y)	7.3 ± 0.42	6.9 ± 0.42	0.44
Literate (%)	89	87	0.66
Indigenous ethnicity (%)[3]	48	51	0.74
Socioeconomic status (%)			
Low	42	28	0.12
Middle	30	30	—
Upper	28	42	—

[1] Baseline characteristics were assessed by using a two-sample Student's t test for continuous variables and a chi-square test of proportions for categorical variables. MM, multiple micronutrient; Fe, iron only.
[2] $\bar{x}$ ± SD (all such values).
[3] Based on the ability to speak or understand an indigenous language (Nahuatl).

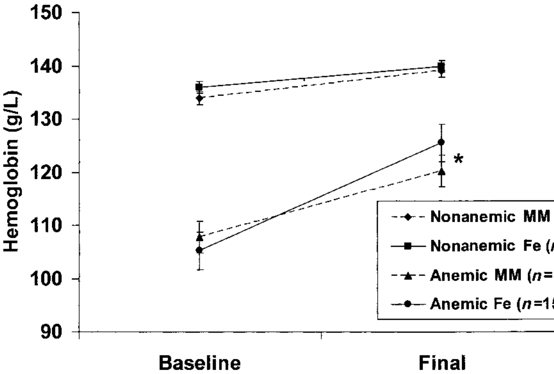

FIGURE 1. Mean (±SE) changes in hemoglobin concentration by treatment group and baseline hemoglobin status. MM, multiple micronutrient group; Fe, iron only group.*Significant interaction between treatment group and baseline hemoglobin, $P < 0.05$.

DISCUSSION

The current study suggests that iron supplementation alone is more effective than is MM supplementation in improving hemoglobin concentrations in anemic nonpregnant women. As was expected (17), the hemoglobin concentration in nonanemic women did not increase over the supplementation period. There has been concern that the nutrients other than iron in the MM supplements could interfere with the absorption of iron and, therefore, that these supplements are not as efficacious in treating anemia (18, 19). Studies have shown that iron absorption is poor in the presence of other minerals such as calcium, magnesium, and zinc (20, 21). The MM supplement used in the current study contained magnesium and zinc, and although we did not measure iron absorption, it may have been low in the MM group because of the presence of these minerals. The confirmation of these results, however, is limited by our lack of data on other indicators of iron status. We also found no additional benefit of hemoglobin concentration in the MM group, which we could have expected as a result of improvements in iron absorption or in red blood cell synthesis because of the inclusion of nutrients such as vitamins A, C, and B-12 and riboflavin and folic acid (22, 23). It is plausible that some of these benefits may have been masked because of the potential inhibitory effects described earlier or that these nutrients were not the cause of anemia in this study population. The latter explanation seems unlikely because previous work suggests that these deficiencies are common in our study population (12, 24). Another concern is the high dose of iron in our supplements, which were originally designed for pregnant women. Although a lower dose of iron (30 mg) would be more appropriate for nonpregnant women, this may have resulted in an even greater inhibitory effect of zinc because of a lower iron:zinc ratio (2:1 compared with 4:1 in the supplement used).

TABLE 3
Hemoglobin concentrations before and after 12 wk of supplementation by treatment group[1]

	MM group (n = 75)	Fe group (n = 77)	P[2]
		g/L	
Baseline	128 ± 13.8	130 ± 15.4	0.48
Final	135 ± 12.7	137 ± 11.7	0.30
Change	6.7 ± 10.6	7.1 ± 13.6	0.84

[1] Values are $\bar{x}$ ± SD.
[2] Two-sample t test.

Few studies have examined the effects of MM supplements on iron status in women of reproductive age (25, 26), and none were found for nonpregnant women. Two studies were conducted in pregnant women, one of which was conducted in the same community as in the present study (26) and another in South Asia (25), where the prevalences of anemia and micronutrient deficiencies are much higher. Both of these studies failed to detect any differences in hematologic indicators between MM and Fe supplements, although there was a suggestion of a lower hemoglobin concentration during midpregnancy in the MM group than in the Fe group in the Mexico study. One of the problems with interpreting these findings is that pregnancy complicates nutrient metabolism combined with the significantly higher requirements of iron and other nutrients (15). Therefore, the current study was conducted in nonpregnant women to determine whether there were differences in the changes in hemoglobin concentration between the 2 treatment groups.

Several iron-supplementation trials have been conducted in nonpregnant women, and the overall reduction in the prevalence of anemia observed in the current study (20.4% at baseline and 10.5% at the end) is comparable with that reported from other studies in semirural communities (27, 28). We were unable to make any conclusions about the true hemoglobin increase and anemia reduction in this sample because of the lack of a true placebo control group. At least part of the increase in hemoglobin concentration from baseline to follow-up may have been due to regression to the mean in both treatment groups. Nonetheless, there is no reason to believe that a regression to the mean would have resulted in differences between the treatment groups; thus, our finding of different benefits from the MM supplement and the iron supplement alone in anemic women should still be valid. Our study had many additional strengths, including its randomized controlled design, low loss to follow-up, high compliance (supervised supplementation), and adequate power.

In future studies it would be beneficial to include other indicators of iron status (such as serum ferritin and serum transferrin receptors) as well as biochemical indicators of the other micronutrients, such as plasma retinol, serum and red blood cell folate, serum vitamin B-12, and serum zinc concentrations. These latter analyses are essential to determining whether MM supplements provide additional benefits, in which case these benefits would need to be weighed against the possibly smaller improvement in hemoglobin concentration. Improving the prepregnancy nutritional status of women for many of these nutrients may confer benefits during subsequent pregnancies and lactation, which are periods of high nutrient demand.

We found that 10% of the women remained anemic at the end of 12 wk. The possibility that this remaining prevalence of anemia may have been due to factors other than iron deficiency, such as infections that contribute to blood and nutrient loss, should be addressed in future studies, as should efforts to prevent and reduce anemia.

SEM-C participated in the study planning and design, data collection and entry, analysis of the data, and writing of the manuscript. UR participated in the study planning and design, data analysis, and writing of the manuscript. LN participated in the study supervision and planning and the writing of the manuscript. JR participated in the study planning and the writing of the manuscript. RM participated in the study planning and design and the writing of the manuscript. None of the authors had any financial or personal conflict of interests.

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