

Multiple micronutrient supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation: a randomized controlled trial in a semirural community in Mexico¹⁻⁴

Usha Ramakrishnan, Teresa González-Cossío, Lynnette M Neufeld, Juan Rivera, and Reynaldo Martorell

ABSTRACT

Background: Little is known about the benefits of prenatal multivitamin and mineral supplements in reducing low birth weight.

Objective: We conducted a randomized, double-blind clinical trial in semirural Mexico to compare the effects of multiple micronutrient (MM) supplements with those of iron supplements during pregnancy on birth size.

Design: Pregnant women ($n = 873$) were recruited before 13 wk of gestation and received supplements 6 d/wk at home, as well as routine antenatal care, until delivery. Both supplements contained 60 mg Fe, but the MM group also received 1–1.5 times the recommended dietary allowances of several micronutrients.

Results: At recruitment, the women in the 2 groups were not significantly different in age, parity, economic status, height, or hemoglobin concentration but differed significantly in marital status (4.6% and 2.0% of women in the MM and iron-only groups, respectively, were single mothers) and mean (\pm SD) body mass index (in kg/m^2 ; 24.6 ± 4.3 and 23.8 ± 3.9 in the iron-only and MM groups, respectively). Losses to follow-up (25%) and compliance (95%) did not differ significantly between the groups. In intent-to-treat analyses (MM group: $n = 323$; iron-only group: $n = 322$), mean (\pm SD) birth weight (2.981 ± 0.391 and 2.977 ± 0.393 kg in the MM and iron-only groups, respectively) and birth length (48.61 ± 1.82 and 48.66 ± 1.83 cm in the MM and iron-only groups, respectively) did not differ significantly between the groups.

Conclusion: These findings suggest that MM supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation. *Am J Clin Nutr* 2003;77:720–5.

KEY WORDS Iron, multivitamins, minerals, supplements, pregnancy, intrauterine growth retardation, Mexico, birth size

INTRODUCTION

At the 1990 World Summit for Children, world leaders set many ambitious nutrition goals to be achieved by the year 2000, and among these was reducing the prevalence of low birth weight (LBW) in developing countries to $< 10\%$ (1). However, estimates of the prevalence of LBW in 1990 and 2000 (17% and 16%, respectively) suggest that little or no progress was achieved (2). Although there is agreement that LBW is an important public health problem because of its marked adverse effects on child survival and on growth and development, there is uncertainty about how best to reduce this problem (3). Poor nutrition is a known

cause of LBW; specifically, short maternal stature, low prepregnant body mass index (BMI; in kg/m^2), and low weight gain are among the most important determinants of LBW (4, 5). Improving the anthropometric status of women would require a mixture of long- and short-term interventions, namely, efforts to prevent growth failure in young girls so that they do not become stunted mothers and interventions to improve diets during pregnancy. Although several efficacy trials showed that food supplementation during pregnancy improves birth weight, programmatic effectiveness has yet to be shown, and the high cost of these programs is a concern (6, 7). Although nutritional education remains a possible intervention, its effectiveness is still to be shown (8).

The possibility that improvements in dietary quality rather than in the quantity of food consumed during pregnancy may be effective in reducing fetal growth retardation has generated considerable excitement among international agencies. A few years ago, the results of a prospective, observational cohort study among teenage mothers in the United States suggested that the use of multiple vitamin and mineral supplements reduces the risk of preterm delivery and LBW (9). A study using a double-blind, placebo-controlled design among HIV-infected but asymptomatic women ($n = 1067$) in Tanzania found that multivitamin supplements dramatically reduce preterm delivery (39%) and LBW (44%) (10). The prevalence of LBW in the 2 groups that received multivitamin supplements with or without vitamin A was only $\approx 9\%$, whereas the prevalence of LBW in the groups that received vitamin A or placebo was 14.5% and 17.2%, respectively. There was no effect of vitamin A, and the mean birth weight of the infants whose mothers received multivitamins was 120 g higher than that of those whose mothers received placebo. Note that all the women received routine iron folate supplements but that none

¹ From the Department of International Health, Rollins School of Public Health, Emory University, Atlanta (UR and RM), and the Centro de Investigación en Nutrición y Salud, Instituto Nacional de Salud Pública, Cuernavaca, Mexico (TG-C, LMN, and JR).

² Presented at the International Union of Nutritional Sciences Congress, August 27–September 1, 2001, Vienna.

³ Supported by the Thrasher Research Fund; UNICEF, New York; Conacyt; and the Instituto Nacional de Salud Pública, Mexico.

⁴ Address reprint requests to U Ramakrishnan, Emory University, Rollins School of Public Health, 1518 Clifton Road, NE, Atlanta, GA 30322. E-mail: uramakr@sph.emory.edu.

Received May 16, 2002.

Accepted for publication July 30, 2002.

TABLE 1
Composition of the prenatal multiple micronutrient supplement¹

Nutrient	Amount
Vitamin A (IU)	2150 [81]
Vitamin D ₃ (IU)	309 [154]
Vitamin E (IU)	5.73 [57]
Thiamine (mg)	0.93 [62]
Riboflavin (mg)	1.87 [134]
Niacin (mg)	15.5 [91]
Folic acid (μg)	215 [54]
Vitamin B-6 (mg)	1.94 [88]
Vitamin B-12 (μg)	2.04 [93]
Vitamin C (mg)	66.5 [95]
Zinc (mg)	12.9 [86]
Iron (mg)	62.4 [208]
Magnesium (mg)	252 [84]

¹Both the intervention and control groups received 60 mg Fe in the form of ferrous sulfate. Percentage of the 1989 US recommended dietary allowance for pregnant women (12) in brackets.

of the supplements contained zinc, which was shown to improve birth weight in some studies (7). Motivated by these results, UNICEF and the World Bank introduced multiple vitamin and mineral supplements in programs for pregnant women and efforts to evaluate the effect of these supplements on birth outcomes, but no results from these efforts are yet available (11). We conducted a double-blind, randomized controlled trial to compare the effects of multiple micronutrient (MM) supplements with those of iron-only supplements during pregnancy on birth outcomes in a semi-rural community in Mexico.

SUBJECTS AND METHODS

Study setting and design

The study was carried out during 1997–2000 near the city of Cuernavaca, in Morelos, Mexico. The study was a collaborative project between the Department of International Health at the Rollins School of Public Health, Emory University, Atlanta, and the Centro de Investigación en Nutrición y Salud, Instituto Nacional de Salud Pública (INSP), Cuernavaca, Mexico. The supplements were prepared and packaged by Laboratorios Zerbóni, SA (Mexico City) with the use of premixes that were specially formulated and provided for the study by Roche (Mexico City). The MM supplement was designed to provide 1–1.5 times the recommended dietary allowances (12) of key vitamins and minerals (*see Table 1* for the actual composition of the supplement) and was similar to supplements that are commercially available, whereas the supplement received by the control group contained only iron, which was consistent with the standard practice of the Ministry of Health in Mexico at the time the study was conducted (13). Both supplements contained 60 mg Fe in the form of ferrous sulfate.

Recruitment of study subjects

All new pregnancies were identified by using a routine, home-based surveillance system in which trained field workers visited all women of reproductive age every 5 wk. The protocol included menstrual history and breast-feeding practices, and possible pregnancies were confirmed by a standard urine test (Gravindex; Ortho Diagnostics Inc, Rariton, NJ), after which the

women were referred to the study physician, who determined study eligibility. Exclusion criteria at recruitment included 1) being at > 13 wk of pregnancy as calculated from the date of the last menstrual period, 2) use of micronutrient supplements, and 3) refusal to participate. The study protocol was approved by the Human Investigations Committee at Emory University and by the INSP. Details of the study protocol were described to eligible women, and written informed consent was obtained by the study physician according to standard procedures. All the women who agreed to participate were then randomly allocated to either the MM or iron-only group. Randomization was carried out by using 4 color-coded groups (2 per treatment) that were assigned a priori with the use of a computer-generated list. Four colors were used to ensure masking and were assigned at random before the study began to a list of serial numbers from 1 to 1000, with the intention to have ≈25% of the subjects assigned to each color; pregnant women were allocated to the preassigned color code as they were added to this list at the time of recruitment. All study personnel and investigators were blinded to the group assignment, the details of which were kept at Emory University and the INSP in sealed envelopes that were opened only after preliminary data analysis was completed.

Data collection

At recruitment, a prenatal examination that included a detailed obstetric history, physical examination, anthropometric assessment, and blood work was carried out by the study physician and a team of trained nurses at the study headquarters. The first supplement was consumed at the study headquarters, after which trained workers visited the women's homes 6 d/wk until delivery to administer supplements and record their consumption. Socioeconomic status was determined by using a questionnaire that included questions regarding education, ethnicity, water and sanitation, quality of housing, household size, occupation, and possessions such as a television set, radio, or bicycle; an index of economic status was derived from these data by using factor analysis similar to that used in previous studies in this setting (14). All subjects were asked to come to the study headquarters for routine prenatal care visits at 26, 32, and 37 wk of pregnancy and at 1 mo after delivery, during which anthropometric measurements and blood samples were also obtained. Anthropometric measurements of height, weight, triceps and thigh skinfold thicknesses, and midupper arm circumference were obtained by highly trained anthropometrists using standard procedures (15). Venous blood samples were collected at baseline and at 32 wk of gestation, and biochemical measurements of micronutrient concentrations (serum ferritin, retinol, folate, and zinc) are currently under way. Hemoglobin concentrations in capillary blood samples obtained by finger prick were measured at the field headquarters by using a HemoCue (HemoCue Inc, Mission Viejo, CA). Appropriate referral and treatment for high-risk pregnancies were provided by the study physician, who worked closely with the local health authorities. All births were followed up by a trained field worker who obtained anthropometric measurements (weight, length, and head circumference) at birth (< 72 h) either at home or at the hospital. Cord blood samples were also obtained in a subsample. All the infants were also followed up until 3 mo of age, and infant growth and feeding practices were monitored at 1, 2, and 3 mo of age. Data entry and checking for errors were carried out on an ongoing basis

TABLE 2
Selected characteristics at recruitment of all the women assigned to receive multiple micronutrient or iron-only supplements during pregnancy¹

	Multiple micronutrients (n = 435)	Iron (n = 438)
Maternal age (y)	23.09 ± 5.48 ² [434]	23.00 ± 5.08 [438]
Time pregnant (wk)	9.24 ± 2.51 [431]	9.31 ± 3.00 [434]
Primipara (%)	36.4 [431]	34.3 [434]
Schooling (y)	6.84 ± 3.41 [396]	7.06 ± 3.23 [404]
Economic status ³	0.00 ± 1.04 [395]	0.08 ± 1.06 [400]
Indigenous ethnicity (%)	32.3 [396]	29.2 [404]
Single mother (%)	4.6 ⁴ [395]	2.0 [404]
Anemia (%)	13.3 [400]	10.2 [405]
Height (cm)	148.66 ± 4.95 [432]	148.55 ± 4.70 [438]
Weight (kg)	52.78 ± 9.67 ⁵ [433]	54.12 ± 9.99 [438]
BMI (kg/m ²)	23.83 ± 3.94 ⁶ [431]	24.51 ± 4.30 [438]

¹n in brackets. Intent-to-treat analysis.

² $\bar{x} \pm$ SD.

³This index was derived by using factor analysis and was based on quality of housing, occupation, and household possessions.

⁴Significantly different from iron. $P = 0.04$ (chi-square test).

^{5,6}Significantly different from iron (Student's t test): ⁵ $P = 0.04$, ⁶ $P = 0.01$.

with supervision by the INSP staff at the INSP headquarters in Cuernavaca. Additional checking of data for errors was carried out at Emory University.

Data analysis

The main outcome variables were measures of birth size (birth weight, length, and ponderal index) and gestational age based on recall of the last menstrual period. In addition, the incidences of preterm delivery (<37 wk of gestation), LBW (<2.5 kg), intrauterine growth retardation (IUGR), and intrauterine stunting (IUS) were also compared between the 2 treatment groups. IUGR and IUS were defined as values below the 10th percentile for the birth weight and birth length, respectively, appropriate for the infant's gestational age and sex from reference data from Miller and Hassanein (16). Anemia and overweight at recruitment were defined by using the World Health Organization definitions of hemoglobin concentration <110 g/L and BMI >25, respectively (17, 18). Compliance was calculated by expressing the total number of tablets consumed as a percentage of the total number of study days in which supplements could have been consumed. We used an intent-to-treat design in which all pregnancies assigned to treatment between July 1997 and 31 December 1999 were included, and the effectiveness of randomization was tested by comparing the 2 groups for selected sociodemographic, health, and nutrition characteristics at recruitment. Comparisons between the final sample with information about birth outcomes and the sample lost to follow-up were also performed for selected baseline characteristics and measures of compliance. The analysis for birth size outcomes was restricted to singleton live births. All comparisons were made by using Student's t tests of means for normally distributed variables and chi-square tests of proportions for categorical variables. Adjusted analyses with multivariate techniques (general linear models and logistic regression) were done to control for factors that differed between groups. In addition, effect modification by characteristics selected before data analysis (maternal BMI at recruitment, infant sex, and socioeconomic

status) was tested for birth weight. All statistical analyses were conducted by using SAS 6.12 (SAS Institute Inc, Cary, NC). Because some of the women had >1 pregnancy, comparisons of the main outcomes of interest were made by using repeated-measures analysis (SAS PROC MIXED). A P value <0.05 was used for all group comparisons.

RESULTS

A total of 921 pregnancies were identified, and for 873 of these pregnancies, the women were assigned to treatment after confirmation, determination of eligibility, and obtaining of informed consent. The comparison of selected maternal characteristics at recruitment shown in **Table 2** indicates that the 2 treatment groups did not differ significantly in most of the characteristics, including age, parity, number of weeks pregnant at study entry, hemoglobin concentration, and maternal height. Almost one-third of the women were overweight, with a significantly higher proportion in the iron-only group (38.8%) than in the MM group (32.3%). Approximately one-third of the pregnancies were primiparous, and the proportion of women who had >1 pregnancy included in the study was 12.6%. The prevalence of anemia at recruitment did not differ significantly between the groups. Because socioeconomic status was measured during the course of the study, data were not available in all cases, especially among women lost to follow-up. However, the groups did not differ significantly in maternal schooling, ethnicity, and economic status. Approximately three-fourths of the women had completed primary school, and 10% had more than a secondary school education. Approximately 30% of the women lived in homes that were made of good-quality construction material. Although most of the women had partners, the proportion of single mothers was significantly higher in the MM group than in the iron-only group.

Data on birth outcomes were available for 656 pregnancies. One-fourth of all the recruited pregnancies were lost to follow-up (217 of 873); the rates of loss were not significantly different between the MM (106/435 = 24.4%) and iron-only (111/438 = 25.2%) groups. Among those lost to follow-up, 41% and 60.4% occurred within the first 4 and 8 wk of supplementation, respectively, and the reasons for these losses were intended and unintended abortions, false-positive test results for pregnancy, dislike of the supplements, and refusal to participate in the study. There were no significant differences between the groups in the percentage of abortions (34% and 28% in the MM and iron-only groups, respectively) or in the percentage of women who disliked the supplements (9.4% and 12.6% in the MM and iron-only groups, respectively). Losses to follow-up that occurred after 20 wk of supplementation did not differ significantly between the groups and were much lower (27/217 = 12.5%) than those that occurred earlier in the study; the reasons for the later losses included migration out of the study area and lack of family support (mother-in-law or spouse did not want them to participate). Of the 656 pregnancies with known birth outcomes, there were 647 live births and 54% were male. The proportion of live births (98.5% in both groups) and of males (52% and 56.5% in the MM and iron-only groups, respectively) did not differ significantly between the groups. There were 5 and 4 stillbirths in the MM and iron-only groups, respectively, and 1 multiple birth (twins) in the iron-only group. The intent-to-treat analysis was restricted to all singleton live births ($n = 645$). The comparison of the final sample of pregnancies with known birth outcomes ($n = 645$) with the pregnancies lost to follow-up ($n = 229$) shown in **Table 3** did not

TABLE 3

Comparison of the final sample of pregnancies with known birth outcomes with the pregnancies lost to follow-up¹

	Final sample (n = 645)	Lost to follow-up (n = 229)
Baseline characteristics		
Maternal age (y)	22.9 ± 5.3 ² [644]	23.6 ± 5.8 [226]
Time pregnant (wk)	9.3 ± 2.4 [642]	9.2 ± 3.6 [221]
Primipara (%)	34.0 [642]	39.4 [221]
Schooling (y)	6.9 ± 3.3 [627]	7.0 ± 3.3 [171]
Economic status ³	0.06 ± 1.03 [624]	-0.01 ± 1.11 [169]
Indigenous (%)	30.1 [627]	32.8 [171]
Single mother (%)	3.2 [626]	3.5 [171]
Anemia (%)	10.9 [598]	14.2 [205]
Height (cm)	148.7 ± 4.8 [643]	148.3 ± 5.0 [228]
Weight (kg)	53.3 ± 9.6 [645]	53.9 ± 10.6 [227]
BMI (kg/m ²)	24.1 ± 4.1 [643]	24.5 ± 4.3 [227]
Intervention		
Duration of supplementation (wk)	28.9 ± 3.4 [645]	8.7 ± 8.8 ⁴ [229]
Supplements consumed (no.)	163.5 ± 21.4 [645]	47.9 ± 47.0 ⁴ [229]
Compliance (%)	94.7 ± 6.1 [645]	82.7 ± 48.0 ⁴ [229]
Multiple micronutrient group (%)	50.1 [645]	48.9 [229]

¹n in brackets. Chi-square tests were used for comparison of categorical variables.

² $\bar{x} \pm SD$.

³This index was derived by using factor analysis and was based on quality of housing, occupation, and household possessions.

⁴Significantly different from the final sample, $P < 0.001$ (Student's *t* test).

indicate any significant differences in baseline characteristics. As expected, compliance and the total number of supplements consumed during the study were significantly lower among the pregnancies lost to follow-up than among the final sample. Weight and length measurements at birth were available for 98.1% ($n = 633$) and 94.1% ($n = 607$) of the pregnancies, respectively; these measurements were taken within 24 h of birth, and >75% of the infants were measured in the first hour in both the MM and iron-only groups. Although 55% of births occurred in area hospitals, 89% of all birth measurements were obtained by the project-trained anthropometrist, and the percentage of birth measurements made by the project-trained anthropometrist did not differ significantly between the 2 groups. In the final sample of pregnancies with known birth outcomes, the groups did not differ significantly in several characteristics, including age, hemoglobin concentration, and compliance, but significant differences in prepregnant weight, BMI, and marital status remained.

Mean values for the main birth outcomes of interest (birth weight, birth length, ponderal index, and gestational age) and commonly used public health outcomes (LBW, IUGR, IUS, and prematurity) are shown in **Table 4**. There were no significant differences between the groups in any of these outcomes. The overall incidences of LBW, preterm delivery, IUGR, and IUS were ≈8.7%, 7%, 10.9%, and 13.0%, respectively. The overall incidence of postterm deliveries (>41 wk of gestation) was 12.3%, and the incidence of postterm deliveries did not differ significantly between the groups. Because of the observed differences in maternal BMI and marital status, the comparisons were also adjusted for these 2 variables, but the results remained unchanged, indicating that MM supplementation in this population had no overall beneficial effect compared with that of iron-only supplementation.

TABLE 4

Comparison of the effect of prenatal multiple micronutrient supplements with that of prenatal iron-only supplements on birth size and gestational age¹

	Multiple micronutrients (n = 323)	Iron (n = 322)
Birth weight (g)	2981 ± 391 ² [318]	2977 ± 393 [315]
LBW (%) ³	8.49 [318]	8.89 [315]
IUGR (%) ⁴	10.09 [317]	11.78 [314]
Birth length (cm)	48.61 ± 1.82 [307]	48.66 ± 1.83 [300]
IUS (%) ⁵	12.75 [306]	13.33 [300]
Ponderal index (kg/m ³)	2.59 ± 0.22 [307]	2.58 ± 0.22 [300]
Gestational age (wk)	39.48 ± 2.25 [321]	39.56 ± 2.26 [321]
Preterm delivery (%) ⁶	7.48 [321]	6.54 [321]

¹n in brackets. LBW, low birth weight; IUGR, intrauterine growth retardation; IUS, intrauterine stunting. There were no significant differences between the groups by repeated-measures analysis.

² $\bar{x} \pm SD$.

³Birth weight < 2500 g.

⁴Defined as below the 10th percentile for birth-weight-for-gestational-age from reference data from Miller and Hassanein (16).

⁵Defined as below the 10th percentile for birth-length-for-gestational-age from reference data from Miller and Hassanein (16).

⁶Less than 37 wk of gestation.

Because some women had >1 pregnancy, repeated-measures analysis was used, and the adjusted mean (\pm SE) differences between the MM and iron-only groups in birth weight, birth length, and ponderal index were 16.1 ± 31 g ($P = 0.60$), -0.002 ± 0.151 cm ($P = 0.99$), and 0.014 ± 0.018 kg/cm³ ($P = 0.42$), respectively. The adjusted odds ratios for the MM group compared with the iron-only group for LBW, IUGR, IUS, and preterm deliveries were 0.98 (95% CI: 0.55, 1.74), 0.82 (95% CI: 0.49, 1.39), 0.96 (95% CI: 0.59, 1.57), and 1.16 (95% CI: 0.60, 2.23), respectively. Testing for interactions that were specified a priori showed no selective effects of treatment by maternal overweight (BMI at recruitment > 25), infant sex, or tertiles of economic status.

DISCUSSION

The findings of this study did not support the hypothesis that multivitamin and mineral supplementation during pregnancy improves birth size in comparison with routine iron supplementation. It is important to recognize that this study was designed as an efficacy trial, and, therefore, problems such as poor availability of supplements and poor compliance, which often affect prenatal care programs in many developing countries (19), were minimized. Bioefficacy was further maximized by early recruitment and direct observation of supplement consumption. Women began consuming supplements around 9 wk of gestation in our study, whereas in programs in many developing countries, supplement consumption typically begins at 16–20 wk (20). Loss to follow-up was higher than originally expected (20%) and may have been due in part to early recruitment. Compliance was high (95%) and did not differ significantly between the intervention groups in the final sample of pregnancies with known birth outcomes. Although the study was not a placebo-controlled trial, the fact that it was a randomized, double-blind controlled trial that compared standard iron with other micronutrients is an important strength (21). The few differences at baseline were addressed in the analysis. Blinding was effective. The comparison of subjects lost to follow-up with those in the final sample also did not suggest differential

losses that may have caused selection bias. Most importantly, the absence of significant findings cannot be attributed to inadequate sample size, which was a limitation in several previous studies of micronutrient supplementation and pregnancy outcomes (22). Actual sample sizes were ≈ 320 per group, exceeding the stipulated sample sizes. A sample size of 250 per group has more than 80% power to detect meaningful effect sizes (0.23 SD) on birth size (100 g and 2.5 cm for birth weight and birth length, respectively) and gestational age (5 d). This sample size also has >80% power to detect a 50% reduction (effect size = 0.28) in the incidence of LBW, IUGR, and IUS, with the assumption of a baseline value of 20% in the control group. However, calculations made after the study showed that the final sample sizes, despite being larger than the stipulated sizes, had inadequate power (<80%) to detect a reduction of 50% in LBW, IUGR, IUS, and prematurity, because the incidence of these outcomes was lower than expected (23).

One possible explanation for the lack of effects is that the extent of micronutrient deficiencies and poor birth outcomes may not have been severe enough to see an effect. Indeed, preliminary analyses suggest that the supplements may not have been efficacious in improving the biochemical status of zinc, iron, and vitamin A (24–26). The explanation for the lack of effects is not that the study population was free of deficiencies. Although the prevalence of anemia in our sample was lower than expected (27), preliminary results showed that iron, zinc, and folate deficiencies each affected 30–40% of the women and that more than one-half of the subjects had ≥ 2 micronutrient deficiencies (28). The prevalence of LBW in our study (8.7%) represents one-half that reported for the control group in the Tanzanian study (17.2%; 10), in which improvements were observed; mean birth weights however, were similar in both the Tanzanian study and our study. As noted earlier, we had expected slightly higher rates of LBW on the basis of earlier estimates (29). Perhaps the provision of high-quality and regular antenatal care, including referrals and treatment of infections, combined with high compliance may have contributed to lower incidences of LBW and anemia. However, antenatal care was provided in Tanzania as well. Other differences between the 2 studies were as follows: 1) the subjects in the Tanzanian study were HIV-positive, which may have affected their response, and 2) the inclusion of zinc in our supplement [zinc supplementation was recently shown in Bangladesh (30) and Peru (31) not to improve birth size] may have interfered with the absorption of other nutrients in the supplement (32).

In summary, the reasons for the lack of improvement in birth size in our study are not clear, and much remains unknown about the effects of MM supplements during pregnancy. The results of other similar trials that are currently underway in different study settings are needed before reaching a conclusion on the role of MM supplements in improving birth size. Even though there were no improvements in birth size, there may have been other benefits such as improvements in maternal nutritional status, maternal and child micronutrient status, and child growth and development. These are being investigated in our ongoing studies of postnatal development. For example, although zinc supplementation during pregnancy failed to reduce the incidence of LBW in Bangladesh, the intervention was associated with reduced morbidity during the first 6 mo of infancy (33). In conclusion, the findings of the present study suggest that among relatively healthy women living in a semirural community in a developing country that is in transition, multivitamin and mineral supplementation

during pregnancy does not improve birth size in comparison with iron-only supplementation. 

As Co-Principal Investigator, UR played a lead role in developing the study proposal and design, implementing the study, checking the data for errors and analyzing the data, interpreting the findings, and writing the final manuscript. TG-C was responsible for implementing the study in Mexico (protocol development, training, and supervision of data collection and entry) and also worked closely with UR in analyzing the data, interpreting the findings, and reviewing the final manuscript. As Technical Coordinator, LMN was responsible for supervising data collection and quality control and for data entry and management in Mexico. She also assisted in checking the data for errors, analyzing the data, and reviewing the final manuscript. As Co-Principal Investigator, JR played a lead role in reviewing the literature, designing and securing funds for the study, implementing the study, interpreting the results, and reviewing the manuscript. As Principal Investigator, RM played a key role in planning and securing funds for the study. He was actively involved in developing the study protocol, monitoring data collection, guiding data analysis, and interpreting the findings, and he assisted in writing the manuscript. None of the authors have any financial or personal interests in any of the organizations that supported the research for this manuscript.

REFERENCES

1. United Nations. World summit for children. World declaration and plan of action for implementing the world declaration on the survival, protection and development of children in the 1990s. New York: United Nations, 1990.
2. ACC/SCN. Fourth report on the world nutrition situation. Geneva: WHO, 2000.
3. Martorell R, Ramakrishnan U, Schroeder DG, Melgar P, Neufeld L. Intrauterine growth retardation, body size, body composition and physical performance in adolescence. *Eur J Clin Nutr* 1998;52: S43–53.
4. WHO. Maternal anthropometry and pregnancy outcomes. A WHO Collaborative Study. *Bull World Health Organ* 1995;73(suppl):1–98.
5. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics* 1987;80:502–11.
6. Kramer MS. Balanced protein/energy supplementation in pregnancy. *Cochrane Database Syst Rev* 2000;2:CD000032.
7. Ramakrishnan U, Neufeld L. Recent advances in nutrition and intrauterine growth. In: Martorell R, Haschke F, eds. *Nutrition and growth*. Nestlé Nutrition Workshop series. Vol 47. Philadelphia: Lippincott Williams and Wilkins, 2001:97–121.
8. Kramer MS. Nutritional advice in pregnancy. *Cochrane Database Syst Rev* 2000;2:CD000149.
9. Scholl TO, Hediger ML, Bendich A, et al. Use of multivitamin/mineral prenatal supplements: influence on the outcome of pregnancy. *Am J Epidemiol* 1997;146:134–41.
10. Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomized trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998;351: 1477–82.
11. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries. Report of a United Nations Children's Fund, World Health Organization, United Nations University workshop held at UNICEF headquarters, New York, July 9, 1999. New York: UNICEF, 1999.
12. National Research Council (US) Subcommittee on the Tenth Edition of the RDAs. Recommended dietary allowances. Washington, DC: National Academy Press, 1989.
13. Dalmiya, N. Progress towards improving iron/folate supplementation programs. New York: UNICEF, 2001.
14. Rivera-Dommarco J, González-Cossío T, Flores M, Hernández-Avila M, Lezana MA, Sepúlveda-Amor J. Emaciación y déficit de talla en menores de cinco años en distintas regiones y estratos en México. (Stunting and emaciation in children under 5 y of age in distinct

- regions and strata in Mexico.) *Salud Publica Mex* 1995;37:95–107 (in Spanish).
15. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Publishers, 1988.
 16. Miller HC and Hassanein K. Diagnosis of impaired fetal growth in newborn infants. *Pediatrics* 1971;48:511–22.
 17. World Health Organization, United Nations Children's Fund, United Nations University. Indicators for assessing iron deficiency and strategies for its prevention. Geneva: World Health Organization, 1998.
 18. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;854:47.
 19. Galloway R, McGuire J. Determinants of compliance with iron supplementation: supplies, side effects, or psychology? *Soc Sci Med* 1994;39:381–90.
 20. Belizan JM, Farnot U, Carroli G, al-Mazrou Y. Antenatal care in developing countries. *Paediatr Perinat Epidemiol* 1998;12:1–3.
 21. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. New York: Van Nostrand Reinhold Company Inc, 1982.
 22. Ramakrishnan U, Manjrekar R, Rivera J, González-Cossío T, Martorell R. Micronutrients and pregnancy outcomes: a review of the literature. *Nutr Res* 1999;19:103–59.
 23. Cohen J. Statistical power analysis for the behavioral sciences. Revised ed. New York: Academic Press, Inc, 1977.
 24. Neufeld LM, Ramakrishnan U, Rivera J, Villalpando S, González-Cossío T, Martorell R. Prevalence of anemia and iron deficiency during pregnancy of women supplemented with iron or iron and multiple micronutrients. *FASEB J* 2001;15:A641 (abstr).
 25. Hernandez-Cordero S, Rivera J, Villalpando S, et al. Multiple micronutrient supplementation during pregnancy: effect on breast milk retinol concentration at one month postpartum. *FASEB J* 2001;15:A642 (abstr).
 26. Garcia-Guerra A, Rivera-Dommarco J, Neufeld LM, González-Cossío T, Ramakrishnan U, Martorell R. Cord blood zinc concentrations from women supplemented with iron or iron and multiple micronutrients during pregnancy. *FASEB J* 2001;15:A641 (abstr).
 27. Martínez H, González-Cossío T, Flores M, Rivera J, Lezana MA, Sepúlveda J. Anemia en mujeres en edad reproductiva, resultados de una encuesta probabilística nacional. (Anemia in women of reproductive age. The results of a national probability survey.) *Salud Publica Mex* 1995;37:108–19 (in Spanish).
 28. Neufeld LM, Ramakrishnan U, González-Cossío T, Rivera J, Martorell R. Prevalence of multiple deficiencies of micronutrients in a semi-rural community in Mexico. IUNS Congress, Vienna, Austria, August 27–September 1, 2001. *Forum of Nutrition*. Vol 56. Basel, Switzerland: Karger (in press).
 29. Schlaepfer L, Infante C. Bajo peso al nacer en México: evidencias a partir de una encuesta retrospectiva a nivel nacional. *Bol Med Hosp Infant Mex* 1995;52:168–79.
 30. Osendarp SJM, van Raaij JM, Arifeen SE, Wahed MA, Baqui AH, Fuchs GJ. A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. *Am J Clin Nutr* 2000;71:114–9.
 31. Caulfield LE, Zavaleta N, Figueroa A, Leon Z. Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. *J Nutr* 1999;129:1563–8.
 32. Whittaker P. Iron and zinc interactions in humans. *Am J Clin Nutr* 1998;68(suppl):442S–6S.
 33. Osendarp SJM, van Raaij JMA, Darmstadt GL, Baqui AH, Hautvast JG, Fuchs GJ. Zinc supplementation during pregnancy and effects on growth and morbidity in low birthweight infants: a randomised placebo controlled trial. *Lancet* 2001;357:1080–5.