Multimicronutrient Supplementation for Undernourished Pregnant Women and the Birth Size of Their Offspring

A Double-blind, Randomized, Placebo-Controlled Trial

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Objective: To evaluate the effect of multimicronutrient supplementation for undernourished pregnant women on the birth size of their offspring, incidence of low-birth-weight infants (<2500 g), and early neonatal morbidity.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Tertiary care hospital.

Participants: Two hundred pregnant women (of 13 465 approached) with a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 18.5 and/or a hemoglobin level of 7 to 9 g/dL were enrolled at 24 to 32 weeks of gestation. One hundred forty-six neonates (73.0%) were available for analysis of birth size and 170 (85.0%) for analysis of morbidity in the 7 days after delivery.

Intervention: The micronutrient supplementation group (n=99) received a multimicronutrient supplement containing 29 vitamins and minerals once a day, from enrollment until delivery (median duration, 58 days; interquartile range, 37-77 days; compliance, 87%). The comparison group (n=101) received placebo for 52 (15-66) days, with 85% compliance. All subjects also received supplements of iron (given in the form of ferrous sulfate, containing 60 mg of elemental iron), 60 mg/d, and folic acid, 500 µg/d.

Main Outcome Measures: Birth weight, length, midarm circumference, incidence of low birth weight, and early neonatal morbidity.

Results: Infants in the micronutrient group were heavier by 98 g (95% confidence interval [CI], –16 to 213 g) and measured 0.80 cm (95% CI, 0.03-1.57 cm) longer and 0.20 cm (95% CI, 0.04-0.36 cm) larger in midarm circumference compared with the placebo group. Incidence of low birth weight declined from 43.1% to 16.2% with multimicronutrient supplementation a (a 70% decrease; relative risk, 0.30; 95% CI, 0.13-0.71; P=.006), and that of early neonatal morbidity declined from 28.0% to 14.8% (a 58% decrease; relative risk, 0.42; 95% CI, 0.19-0.94; P=.04).

Conclusion: Compared with iron and folic acid supplementation, the administration of multimicronutrients to undernourished pregnant women may reduce the incidence of low birth weight and early neonatal morbidity.

Arch Pediatr Adolesc Med. 2007;161:58-64

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L OW BIRTH WEIGHT (LBW) (<2500 g) is a major predictor of neonatal and infant mortality.[1] Intrauterine growth retardation, rather than prematurity, is the principal cause of LBW in South Asian countries.[2] Infants who are small or disproportionate in size at birth also have an increased risk of developing coronary heart disease, type 2 diabetes mellitus, stroke, and hypertension during adult life. It is postulated that these diseases are programmed by inadequate supply of nutrients to the developing fetuses (the Barker hypothesis).[3] Thus, measures to increase the size of infants at birth constitute a priority area in developing nations.

Prepregnancy and maternal undernutrition are important predictors of reduced birth weight in resource-poor settings.[1,2,4] It now appears that several

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nutrient factors, including both macronutrients and micronutrients, may be deficient in mothers in developing countries.[5,6] The habitual diet of women be-

longing to low-income groups is deficient not only in calories and proteins but also in vitamin C, vitamin E, folate, vitamin B complex, and trace elements such as iron, zinc, magnesium, manganese, and selenium. In a study of 513 pregnancies in Hackney, England, Doyle et al[7] reported that mothers who subsequently gave birth to LBW infants had low intake of 43 of 44 nutrients, including copper, zinc, magnesium, vitamin A, vitamin C, vitamin E, and vitamin B complex. Another study of rural Indian women documented a strong relationship between infant birth weight and the mother's intake of foods rich in micronutrients, suggesting that these may be important limiting factors for fetal growth in undernourished mothers.[5]
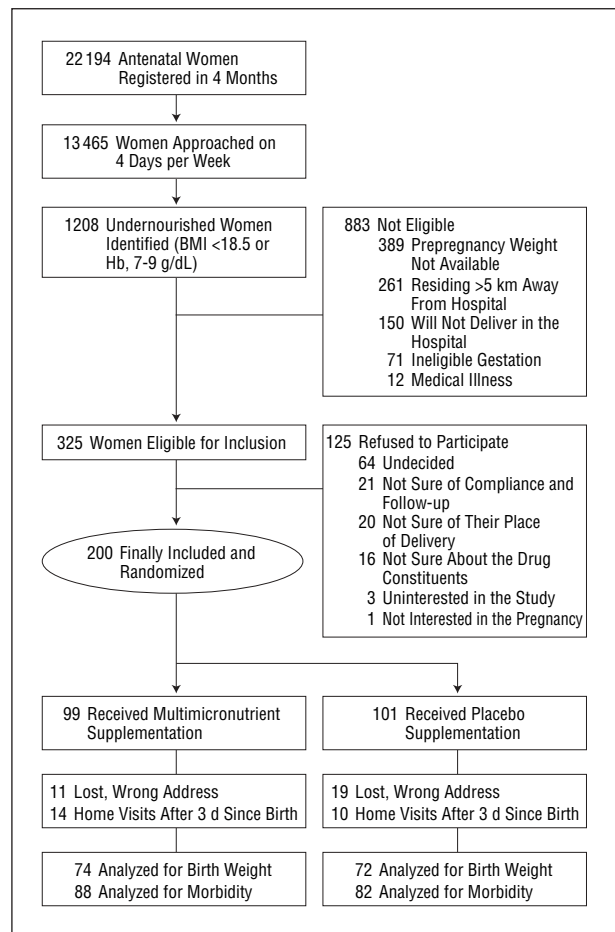
Compared with iron and folic acid supplementation, community-based studies in Nepal[8] and Mexico[9] have failed to document an increase in birth weight or a decline in the incidence of LBW after antenatal multimicronutrient supplementation. On the other hand, recent trials conducted by Osrin et al[10] in Nepal and Kaestel et al[11] in Guinea-Bissau demonstrated an increase in the birth size with antenatal multimicronutrient supplementation. Friis et al[12] conducted another randomized trial in Zimbabwe and concluded that antenatal multimicronutrient supplementation may be one strategy to increase birth size, although their results failed to achieve a statistically significant difference. However, these trials did not selectively target undernourished pregnant women who are at greater risk for delivering infants with lower birth size. We therefore evaluated the effect of multimicronutrient supplementation in undernourished pregnant women on birth size and early neonatal morbidity.

Figure 1. Study flow chart. BMI indicates body mass index (calculated as weight in kilograms divided by the square of height in meters); Hb, hemoglobin level.

METHODS

The study was designed as a randomized, double-blind, placebo-controlled trial conducted in a tertiary care hospital of East Delhi, India, from May 1, 2002, to April 30, 2003. The hospital serves poor residents living in nearby urban slums and families from surrounding rural communities. A clearance was obtained from the ethical committee of the Sitaram Bhartia Institute of Science and Research, New Delhi, India. The study protocol was fully explained to the participants, and informed signed consent was obtained.

ENROLLMENT

The sample size was calculated from a community-based, longitudinal study of pregnant rural Indian women correlating the intake of micronutrient-rich foods with the birth weight of their offspring.[5] A total of 100 women in each group were required to detect a difference of 150 g in mean birth weights (estimated SD, 350 g for each group) with a significance level of .05 and a power of 80% after allowing for a 20% loss to follow-up. Thus, we enrolled 200 pregnant women (age range, 18-44 years) of any gravidity with a period of gestation ranging from 24 to 32 weeks, carrying a singleton pregnancy, and having a body mass index (calculated as weight in kilograms divided by the square of height in meters) of less than 18.5 and/or a hemoglobin level of 7 to 9 g/dL from our antenatal clinic (**Figure 1**). Only women residing within 5 km of the hospital and planning to deliver in the hospital or in the neighborhood were enrolled. Women with the following established medical risk factors for having reduced or excessive birth weight of the neonate were excluded: hypertension, renal disease, heart disease, diabetes mellitus, urinary tract infection, tuberculosis, smoking, alcohol intake, or chronic intake of other drugs. Women already receiving iron and folic acid or other micronutrient tablets were also excluded.

INITIAL DATA COLLECTION

Baseline data collected included name, age, address, telephone number, religion, education, occupation, obstetric history, parity, family income, and the number of family members. Gestational age was calculated by last menstrual period and clinical evaluation. The woman's typical daily activity was recorded as domestic or outdoor. Prepregnancy weight was obtained by checking the previous health records or by recall. Present weight was recorded on a standardized bathroom scale to the nearest 0.5 kg. Height was measured to the nearest 0.1 cm. The body mass index was calculated by dividing the prepregnancy weight in kilograms by the square of the height in meters. Hemoglobin levels were measured using the Sahli method and recorded in grams per deciliter. The same observer (M.R.) obtained all of the measurements.

RANDOMIZATION AND BLINDING

Participants were randomized to receive the multimicronutrient supplementation (micronutrient group) or the placebo (pla-

cebo group) from 24 to 32 weeks of gestation onward. Allocation was based on a 2-step simple randomization. Subjects were first allocated (by computer-generated random sequence) to be in 1 of 10 blocks of 20 subjects each. These blocks were coded as 1 to 10 in a random manner. Of 1 to 10, 5 blocks were randomly assigned to receive the placebo and the rest to receive the multimicronutrient tablets. Tablets were kept in containers marked 1 to 10. A participant received the drug from 1 of these 10 containers per allocation. Allocation was concealed by the use of sealed envelopes. The caregiver and the subject were blinded regarding the content of the tablet being given. Randomization, coding, allocation concealment, and blinding was performed by one of us (R.K.), and the drugs were dispensed by another (M.R.). The multimicronutrient tablet contained the following: beta carotene (vitamin A), concentrated in 2500 IU; thiamine mononitrate (vitamin B_1), 1 mg; riboflavin (vitamin B_2), 1.5 mg; pyridoxine hydrochloride (vitamin B_6), 1 mg; cyanocobalamin (vitamin B_{12}), 1 µg; ascorbic acid (vitamin C), 50 mg; cholecalciferol (vitamin D_3), 200 IU; tocopherol acetate (vitamin E), 7.5 mg; calcium pantothenate, 5 mg; folic acid, 0.15 mg; nicotinamide (niacinamide), 20 mg; biotin, 30 µg; zinc, 15 mg; potassium iodide, 0.15 mg; ferrous fumarate, 10 mg; magnesium oxide (light), 100 mg; manganese sulfate, 2.5 mg; copper, 2 mg; calcium, 162 mg; phosphorus, 125 mg; potassium, 40 mg; chloride, 36.3 mg; chromium, 25 µg; molybdenum, 25 µg; sodium selenate, 30 µg; nickel, 5 µg; silicon dioxide, 2 mg; vanadium, 10 µg; and boron, 150 µg. The placebo tablet consisted of calcium with chocolate flavor and color.

The supplement and the placebo looked and tasted alike. Participants and the physicians were unaware of group allocation. The code key was opened only after the intervention, data collection, follow-up, and tabulation were finished.

INTERVENTION

Pregnant women were advised to take the supplement once a day, 30 minutes after meals. Tablets were given to the participants on a fortnightly basis and they were asked to maintain a record of tablet consumption. All participants were advised concerning a proper diet (based on the Indian Council of Medical Research recommendation for pregnant women),[13] administered iron (given in the form of ferrous sulfate, containing 60 mg of elemental iron) and folic acid supplements in the usual dosages, ie, 60 mg/d and 500 µg/d, respectively, and given routine antenatal advice, immunization, and health education. Supplementation continued until delivery. At each antenatal visit, the participants were questioned regarding tablet intake, compliance, and adverse effects. The number of tablets consumed was cross-checked by observing the remaining number of tablets in each pack. Compliance was defined as the percentage of tablets consumed by each participant compared with the number of days the drug was advised to be taken.

CLINICAL MONITORING

Clinical monitoring was performed during each antenatal visit, eg, every 4 weeks until 36 weeks of gestation and then weekly until delivery. Maternal weight gain was recorded. The presence of edema, gestational hypertension, preeclampsia, antepartum hemorrhage, fever, urinary tract infection, preterm labor, premature rupture of membranes, diarrhea, gestational diabetes, drug intake, and any decrease in fetal movements was recorded. If the participant failed to appear within 1 week of her expected antenatal follow-up, she was contacted by mail or by telephone. All clinical decisions regarding management, timing of delivery, etc, were made by the attending faculty and

staff of the Department of Obstetrics and Gynecology, University College of Medical Sciences, Delhi.

FINAL DATA COLLECTION AT DELIVERY

All efforts were made to have the mother deliver at the hospital. The date and time of delivery, maternal weight and gestational age at delivery, mode of delivery, and any complications during or after delivery, including premature rupture of membranes, antepartum hemorrhage, preeclampsia, toxemia, fetal distress, birth asphyxia, and meconium staining, were recorded. In case of home delivery, the mother was contacted personally and details regarding the delivery were obtained.

NEONATAL CHARACTERISTICS

Gestational age was calculated using the new Ballard score.[14] Apgar scores were recorded in hospital deliveries. The newborn was labeled according to gestational age as term (37-41 weeks), preterm (<37 weeks), or post term (≥42 weeks). Birth weight was recorded within 30 minutes for institutional deliveries and at the first contact after birth (within 3 days) for home deliveries. An electronic weighing scale (Seca, Hamburg, Germany) was used to record the weight to the nearest 5 g. Neonatal crown-to-heel length was measured to the nearest 0.1 cm using an infantometer, with the infant supine, the neck fully extended, the soles of feet held firmly against the footboard, and the head touching the fixed board. Midarm circumference was measured to the nearest 0.1 cm in the left upper arm, midway between the acromion and olecranon processes. A standardized fiberglass tape was used. Neonates weighing less than 2500 g were designated as LBW, irrespective of gestation. In addition, they were classified as being small (SGA), appropriate, or large for gestational age according to the chart of intrauterine growth by Lubchenco et al.[15]

Newborns delivered at the hospital were followed up for the first 7 days to document any evidence of congenital anomaly, sepsis (clinically suspected or culture proved), respiratory distress (respiratory rate of >60/min, retractions, or grunt), diarrhea, vomiting or abdominal distention, jaundice, convulsions, bleeding, hypothermia, skin boils, and any other morbidity. Standard definitions based on the recommendations of the National Neonatology Forum of India were used for defining neonatal morbidities.[16] In case of death of the newborn, the most probable cause of death was recorded per the attending clinician's diagnosis. Those women who delivered at home were asked for any history of neonatal illness, clinic visit, or hospitalization during the first week after birth. The cause of death was ascertained by verbal autopsy.

STATISTICAL ANALYSIS

Data were analyzed on an intention-to-treat basis.[17] Birth weight was the primary outcome variable. Secondary outcome measures included length and midarm circumference at birth, incidence of LBW and SGA infants, and early neonatal morbidity. Baseline variables and outcome measures were compared by the unpaired t test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. To assess between-group differences, multiple regression analysis was performed for continuous dependent variables (ie, birth weight, length, and midarm circumference). Logistic regression analysis was used when the dependent variable was dichotomous, ie, incidence of LBW, SGA, and early neonatal

Table 1. Baseline Maternal Characteristics in the Micronutrient and Placebo Groups*

Maternal Variable	Micronutrient Group (n = 99)	Placebo Group (n = 101)	P Value
Maternal age, y	23.4 (3.2)	23.1 (3.0)	.39
Monthly family income, rupees	3955 (1492)	3565 (1369)	.06
Parity	0.8 (0.7)	0.7 (0.7)	.64
Prepregnancy weight, kg	39.4 (3.6)	38.4 (3.9)	.06
Enrollment weight, kg	42.6 (3.7)	41.5 (4.0)	.05
Enrollment gestation, wk	27.9 (2.5)	27.8 (2.7)	.55
Height, cm	155.2 (3.4)	154.7 (3.3)	.29
BMI	16.3 (1.5)	16.0 (1.5)	.12
Hemoglobin level, g/dL	9.4 (1.3)	9.5 (1.2)	.60
Residence in slum, No. (%)	94 (94.9)	98 (97.0)	.45
Hindu, No. (%)	88 (88.9)	89 (88.1)	.86
Illiterate, No. (%)	20 (20.2)	29 (28.7)	.16
Domestic physical activity, No. (%)	98 (99.0)	98 (97.0)	.51
Bad obstetric history, No. (%)	7 (7.0)	16 (15.8)	.05
Hemoglobin level <9 g/dL, No. (%)	40 (40.4)	40 (39.6)	.91
BMI <18.5, No. (%)	93 (93.9)	97 (96.0)	.36

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
*Unless otherwise indicated, data are expressed as mean (SD).

morbidity. Independent factors adjusted for each of the dependent variables included family income, maternal age, prepregnancy weight, parity, maternal height, maternal hemoglobin level, sex of the newborn, and gestational age at delivery. Statistical significance was defined as a 2-tailed $P<.05$. Analysis was performed using SPSS+, version 13.0 (SPSS Inc, Chicago, Ill).

RESULTS

Two hundred undernourished pregnant women were included in the trial after providing written informed consent (Figure 1). Participants were randomized to receive multimicronutrient supplementation (n=99) or placebo (n=101). Baseline characteristics of the enrolled subjects were comparable in both groups (**Table 1**).

Subjects in the micronutrient group received supplementation for a mean (SD) duration of 54.5 (27.6) days (median, 58 days; interquartile range, 37-77 days) compared with the placebo group, who received the drugs for a mean (SD) duration of 45.1 (29.4) days (median, 52 days; interquartile range, 15-66 days) ($P=.02$). The actual duration of supplementation in the 2 groups is shown in **Table 2**. Median compliance in the micronutrient and placebo groups was 87% and 85%, respectively. Adverse effects of the supplementation (nausea, vomiting, diarrhea, abdominal pain, and anorexia) were seen in 7 subjects in the micronutrient group and 13 in placebo group. None of the adverse effects necessitated discontinuation of supplementation.

Complications of pregnancy occurred in 3 subjects in the micronutrient group and 4 in the placebo group ($P=.71$). Pregnancy-induced hypertension was detected in a total of 5 women, including 2 in the micronutrient group and 3 in the placebo group. Infections (ie, urinary tract, tuberculosis, or respiratory tract) were documented in 1 subject in the micronutrient group and 2 in the placebo group. Women in the micronutrient group

**Table 2. Subjects Receiving Supplementation in the Study Groups**

Duration of Supplementation, d	No. (%)		P Value
	Micronutrient Group (n = 99)	Placebo Group (n = 101)	
0	10 (10.1)	17 (16.8)	.16
1-25	5 (5.1)	10 (9.9)	.19
26-50	22 (22.2)	23 (22.8)	.93
51-75	35 (35.4)	35 (34.7)	.92
76-90	21 (21.2)	12 (11.9)	.08
>90	6 (6.1)	4 (4.0)	.50

gained a mean (SD) weight of 9.2 (2.8) kg during pregnancy compared with 8.7 (2.9) kg in the placebo group ($P=.26$). The mean (SD) gestational ages at delivery were 39.6 (1.4) and 39.6 (1.4) weeks in the micronutrient and placebo groups, respectively ($P=.9$).

Delivery details were available for 170 cases. Of these, 134 (78.8%) delivered in the hospital, whereas 36 (21.2%) delivered at home. Of these 170 infants, 45 (51%) of 88 in the micronutrient group and 42 (51%) of 82 in the placebo group were boys. The proportion of home deliveries was also comparable in both groups (micronutrient group, 20 [23%]; placebo group, 16 [19%]; $P=.71$). Only 5 women required assisted or operative intervention during delivery (3 in the micronutrient group and 2 in the placebo group). Complications of delivery were present in 13 (15%) of 88 cases in the micronutrient group compared with 10 (12%) of 82 in the placebo group ($P=.66$). Birth weight and details of morbidity in the first week of life were available for 146 and 170 neonates, respectively. A comparison of baseline variables between those available (n=146) and those lost to follow-up (n=54) revealed that women who dropped out of the study had a lower family income (mean [SD], 2972 [1070]

rupees) compared with those who were included in the final analysis (mean [SD], 4048 [1454] rupees) (P<.001). No other baseline variable differed between those undergoing analysis and those lost to follow-up.

The birth weights ranged from 750 to 3500 g. Only 2 infants were preterm (gestational ages, 32 and 31 weeks) and weighed 750 and 950 g, respectively (1 infant in each group). The distribution of birth weights between the micronutrient and placebo groups is provided in **Figure 2**. After adjusting for 8 potential confounding factors, birth weight in the micronutrient group was 98 g (range, −16 to 213 g) higher than in the placebo group; the effect size was small with a wider confidence interval. Neonates in the micronutrient group measured 0.8 cm longer and 0.2 cm larger in midarm circumference (**Table 3**). The proportion of LBW infants decreased by 70% in the micronutrient group. The proportion of SGA infants also decreased by 55% in the micronutrient group (Table 3). Furthermore, multiple regression analysis in the micronutrient group showed that the duration of multimicronutrient supplementation and compliance demonstrated a significant positive correlation with birth size (**Table 4**). Women who were anemic (using the World Health Organization cutoff for hemoglobin level of 11 g/dL in pregnant women) were not likely to benefit more from multimicronutrient supplementation, in terms of birth size. Also, there was no significant difference between birth
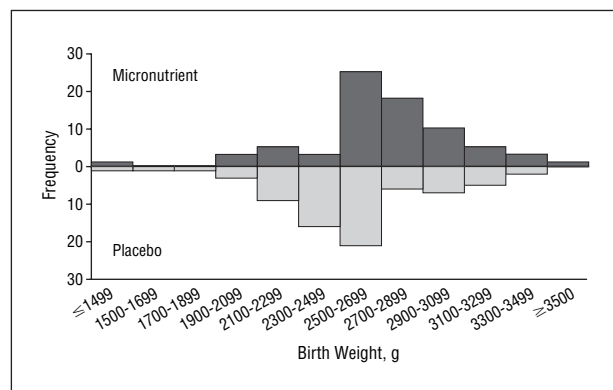
size for women with hemoglobin levels of less than 9 g/dL and the rest in the micronutrient group (data not shown).

Morbidities were present in 36 (21.2%) of 170 neonates during the first week of life. The total number of illnesses was 41 because some neonates had more than 1 illness. The number of illnesses in the micronutrient and placebo groups was 15 (sepsis, 11; others, 4) and 26 (sepsis, 19; others, 7), respectively. The incidence of early neonatal morbidity was almost double in the placebo group compared with the micronutrient group (Table 3). Birth weight correlated very strongly with neonatal morbidity when included in the multivariate model, eliminating the group effect (P<.001). A total of 8 infants died, 4 in each group (relative risk, 0.93; 95% confidence interval, 0.24-3.61; P=.92). Causes of death were similar in the 2 groups and included sepsis in 4 and asphyxia/intracranial bleeding in the rest.

COMMENT

We examined the effect of multimicronutrient supplementation in pregnant undernourished women on the birth size of their infants and the incidence of LBW in a hospital-based study in a setting where the incidence of LBW is more than 30%.[1] We concluded that multimicronutrient supplementation targeted at pregnant undernourished women may decrease the incidence of LBW infants, despite no statistically significant change in birth weight. This translated into significantly lower neonatal illnesses during the first week of life in the micronutrient group. There was no effect on the duration of gestation.

The major strength of the present study was its focused approach. Supplementation was restricted to a relatively homogeneous group of undernourished pregnant women from an urban poor population who are likely to show the maximum benefit of such an intervention. Limitations include a large loss to follow-up (27.0%), limited power of the study to detect small changes in birth size, and the lack of data on late neonatal morbidity and perinatal mortality. The study population from urban slums is migratory, and it is typical for them to change homes,

Figure 2. Bihistogram depicting distribution of birth weights in the micronutrient and placebo study groups.

Table 3. Neonatal Anthropometry, Incidence of LBW, and Early Neonatal Morbidity and Mortality in the Study Groups

Neonatal Characteristics	Micronutrient Group (n = 74)	Placebo Group (n = 72)	Difference* or Relative Risk† (95% CI)		P Value	
			Unadjusted	Adjusted‡	Unadjusted	Adjusted
Anthropometry, mean (SD)						
Birth weight, g	2666.6 (372.6)	2510.7 (419.0)	155.9 (26 to 285)	98 (−16 to 213)	.02	.09
Length, cm	48.6 (2.0)	47.2 (3.0)	1.37 (0.52 to 2.21)	0.80 (0.03 to 1.57)	.002	.04
Midarm circumference, cm	9.3 (0.4)	9.0 (0.6)	0.32 (0.13 to 0.44)	0.20 (0.04 to 0.36)	.001	.02
Gestational age at delivery, wk§	39.6 (1.4)	39.6 (1.4)	0.02 (−0.41 to 0.44)	0.01 (−0.44 to 0.45)	.94	.99
Neonatal outcome, No. (%)§						
LBW infants	12/74 (16.2)	31/72 (43.1)	0.38 (0.21 to 0.67)	0.30 (0.13 to 0.71)	.001	.006
SGA[15] infants	23/74 (31.1)	37/72 (51.4)	0.61 (0.40 to 0.91)	0.45 (0.21 to 0.97)	.04	.04
Sick newborns	13/88 (14.8)	23/82 (28.0)	0.53 (0.29 to 0.97)	0.42 (0.19 to 0.94)	.01	.04

Abbreviations: CI, confidence interval; LBW, low-birth-weight (<2500 g); SGA, small for gestational age.
*Calculated as the difference between study groups.
†Calculated as the relative risk between study groups.
‡Adjusted for maternal age, family income, parity, prepregnancy weight, height, hemoglobin, neonatal sex, and gestational age at delivery.
§Gestational age at delivery was replaced by birth weight as an independent variable when the dependent variable was gestational age.

Table 4. Correlation of Birth Size With Duration of Supplementation and Compliance in the Micronutrient Group

Dependent Variable	Variable Adjusted*	Duration of Supplementation			Compliance		
		Regression Coefficient	Variance Explained	P Value	Regression Coefficient	Variance Explained	P Value
Birth weight	Gestational age	9.24	0.32	<.001	12.35	0.24	.001
Length	Family income	0.04	0.31	<.001	0.07	0.26	.001
Midarm circumference	Family income	0.01	0.33	<.001	0.02	0.24	.001

*Only the maternal variables that correlated positively with birth size were adjusted.

which is primarily dictated by job requirements. Also, certain women preferred to deliver at home because of being too late in labor to be brought to a hospital, the unavailability of transportation at the right time, the proximity of a traditional birth attendant nearby, or family circumstances. We acknowledge this as a reality for such trials conducted in the developing world. Also, we did not evaluate the dietary intake of the study subjects. It should be kept in mind that the comparisons refer to multimicronutrient vs iron and folic acid supplementation, rather than placebo, because of ethical reasons, and thus the results may be an underestimation of the potential benefit compared with no supplementation at all. Also, at the conclusion of the study, women were not asked to estimate whether they received the multimicronutrient supplement or the placebo, to test whether the products were indistinguishable.

We provided a multimicronutrient supplement that contained all of the 15 micronutrients suggested by the expert group of the World Health Organization and the United Nations Children's Fund for supplementation in pregnancy.[18] Our supplement provided an additional 14 micronutrients. This supplement combination is in close proximity to the US and Canadian recommended daily adult reference requirements for each nutrient. Another reason for choosing this supplement combination was that it was readily available in the Indian market. The supplement was given only during the last trimester of pregnancy because of logistic constraints. The United Nations Children's Fund has suggested that multimicronutrient supplementation should be given throughout the pregnancy. We are interested in knowing the impact of a longer supplementation schedule, because the duration of supplementation was significantly related to all of the outcome variables.

The impact of multimicronutrient supplementation on birth weight and the incidence of LBW and SGA infants were markedly stronger in our trial compared with the Nepal study,[10] in which micronutrient supplementation resulted in a 25% reduction in LBW. The reason was our targeted approach of supplementation only in women at risk of producing LBW infants. The failure of most community-based trials[8,9] to document the beneficial effect of multimicronutrient supplementation on increasing birth weight suggests the need for an approach focused on women at risk for producing a small infant.

An increase in birth weight is assumed to be associated with better infant survival. However, Christian et al[19] have cautioned that the increase in birth size or decrease in the incidence of LBW as a result of antenatal multimicronutrient supplementation may not have the desired biological effect. They pooled the data of 2 Nepal trials to report an association between multimicronutrient supplementation and decreased perinatal and neonatal survival, despite the association with increased birth weight. It may be premature to generalize their apprehensions, but this aspect definitely needs further exploration. Another important outcome requiring study is reduction in the burden of premature deliveries.

Our findings are of a preliminary nature and need to be further corroborated. We advocate community-based trials in deprived populations to ascertain the impact of a supplementation schedule lasting throughout pregnancy. The sample size should be large enough to evaluate the effect of such supplementation on neonatal morbidity and mortality, in addition to the size at birth.

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Author Contributions: All authors approved the final version of this article. *Study concept and design:* Gupta, Ray, Dua, Radhakrishnan, Kumar, and Sachdev. *Acquisition of data:* Ray and Radhakrishnan. *Analysis and interpretation of data:* Gupta, Ray, Radhakrishnan, Kumar, and Sachdev. *Drafting of the manuscript:* Gupta, Ray, Dua, Radhakrishnan, Kumar, and Sachdev. *Critical revision of the manuscript for important intellectual content*: Sachdev. *Statistical analysis:* Gupta, Kumar, and Sachdev. *Administrative, technical, and material support:* Gupta, Ray, and Radhakrishnan. *Study supervision:* Gupta, Dua, and Radhakrishnan.

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