ORIGINAL ARTICLE

Vitamins and Perinatal Outcomes among HIV-Negative Women in Tanzania

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ABSTRACT

BACKGROUND

Prematurity and low birth weight are associated with high perinatal and infant mortality, especially in developing countries. Maternal micronutrient deficiencies may contribute to these adverse outcomes.

METHODS

In a double-blind trial in Dar es Salaam, Tanzania, we randomly assigned 8468 pregnant women (gestational age of fetus, 12 to 27 weeks) who were negative for human immunodeficiency virus infection to receive daily multivitamins (including multiples of the recommended dietary allowance) or placebo. All the women received prenatal supplemental iron and folic acid. The primary outcomes were low birth weight (<2500 g), prematurity, and fetal death.

RESULTS

The incidence of low birth weight was 7.8% among the infants in the multivitamin group and 9.4% among those in the placebo group (relative risk, 0.82; 95% confidence interval [CI], 0.70 to 0.95; P=0.01). The mean difference in birth weight between the groups was modest (67 g, P<0.001). The rates of prematurity were 16.9% in the multivitamin group and 16.7% in the placebo group (relative risk, 1.01; 95% CI, 0.91 to 1.11; P=0.87), and the rates of fetal death were 4.3% and 5.0%, respectively (relative risk, 0.87; 95% CI, 0.72 to 1.05; P=0.15). Supplementation reduced both the risk of a birth size that was small for gestational age (<10th percentile; 10.7% in the multivitamin group vs. 13.6% in the placebo group; relative risk, 0.77; 95% CI, 0.68 to 0.87; P<0.001) and the risk of maternal anemia (hemoglobin level, <11 g per deciliter; relative risk, 0.88; 95% CI, 0.80 to 0.97; P=0.01), although the difference in the mean hemoglobin levels between the groups was small (0.2 g per deciliter, P<0.001).

CONCLUSIONS

Multivitamin supplementation reduced the incidence of low birth weight and small-for-gestational-age births but had no significant effects on prematurity or fetal death. Multivitamins should be considered for all pregnant women in developing countries. (ClinicalTrials.gov number, NCT00197548.)

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Worldwide, approximately 20 million children each year are born weighing less than 2500 g; these births constitute 15.5% of all births, and 96.0% of infants with low birth weight are in developing countries.[1] Low birth weight is associated with perinatal and infant mortality,[2] stunting by reproductive age,[3] and chronic diseases, including coronary heart disease and diabetes.[4]

The micronutrient status of the mother is an important determinant of fetal growth and survival.[5] Iron and folate supplements are routinely provided to pregnant women in many developing countries.[6,7] The prenatal dietary intake of other micronutrients is frequently considered to be insufficient to meet increased requirements during pregnancy, particularly in developing countries.[8] Prenatal multivitamin supplements are routinely provided in many developed countries; however, this practice is not based on findings from randomized trials. Two placebo-controlled trials involving pregnant women in Sarlahi, Nepal,[9] and in Mexico,[10] most of whom presumably were negative for human immunodeficiency virus (HIV) infection, showed no significant effects of micronutrient supplements on birth weight or other pregnancy outcomes. In a trial conducted in Janakpur, Nepal, supplements reduced the incidence of low birth weight but had no effect on preterm birth.[11] Pooled analyses of data from the two trials in Nepal suggest that micronutrient supplementation may increase the risk of perinatal death.[12]

In a randomized, controlled trial involving HIV-positive pregnant women in Tanzania, multivitamin supplements significantly reduced the risks of fetal death, low birth weight, and preterm birth and increased maternal CD4 cell counts and hemoglobin levels.[13] Because these benefits might not apply to HIV-negative women, we conducted a similarly designed trial involving HIV-negative women in Tanzania to assess the effects of these supplements on birth outcomes and maternal health indicators.

METHODS

PATIENTS

Pregnant women who attended antenatal clinics in Dar es Salaam, Tanzania, between August 2001 and July 2004 were invited to participate in the trial. Requirements for eligibility included a negative test for HIV infection, a plan to stay in the city until delivery and for 1 year thereafter, and an estimated gestational age between 12 and 27 weeks according to the date of the last menstrual period. HIV type 1 serologic status was ascertained from all women who consented to participate in the trial by means of two sequential enzyme-linked immunosorbent assay tests.[14] All women provided written informed consent to participate. The study was approved by the institutional review boards at Muhimbili University College of Health Sciences in Dar es Salaam and at the Harvard School of Public Health in Boston.

STUDY DESIGN

The women were randomly assigned to receive a daily oral dose of either a multivitamin supplement or placebo from the time of enrollment until 6 weeks after delivery. The supplements included 20 mg of vitamin B_1, 20 mg of vitamin B_2, 25 mg of vitamin B_6, 100 mg of niacin, 50 μg of vitamin B_{12}, 500 mg of vitamin C, 30 mg of vitamin E, and 0.8 mg of folic acid. On average, these amounts were twice the recommended dietary allowance (RDA) for vitamin E and 6 to 10 times the RDA for vitamin C and several B vitamins. Vitamin A and zinc were not included because earlier studies had shown harmful effects of vitamin A during pregnancy and at delivery in HIV-infected women in Tanzania[15] and Zimbabwe,[16] and several trials of zinc administered prenatally had shown no evidence of a benefit.[17] The active tablets and placebo were similar in shape, size, and color and were packaged in identical coded bottles. A list was prepared according to a randomization sequence in blocks of 20; at enrollment, each eligible woman was assigned to the next numbered bottle. At every monthly visit, a new bottle was given to each woman, and the pills remaining in the used bottles were counted. Research assistants who assessed the study outcomes were unaware of the intervention groups. Tishcon commercially prepared the tablets but had no involvement in the study design, implementation, or reporting of the findings.

Our research team provided the participants with standard prenatal care. All women, irrespective of the assigned study regimen, were given daily doses of iron (60 mg of elemental iron) and folic acid (0.25 mg). They were also given malaria prophylaxis in the form of sulfadoxine–pyrimethamine tablets (Fansidar, Roche) at 20 weeks and 30 weeks of gestation. All women completed a baseline questionnaire that included their socio-

demographic characteristics and obstetrical history. At randomization and at monthly visits thereafter, questionnaires were administered to evaluate interim medical problems. Laboratory investigations at baseline included tests for syphilis, gonorrhea, and trichomoniasis; routine urine and stool tests; and evaluation of blood films for malaria. The total and differential white-cell counts were calculated with the use of a CBC5 counter (Coulter). Counts of T-cell subgroups (CD4+, CD8+, and CD3+) in a random sample of women were calculated with the use of the FACScount or FACScan system (Becton Dickinson). Blood counts were obtained at baseline and 6 weeks post partum. The laboratory results were available to the women's physicians, who prescribed treatment, if indicated.

Full-time research midwives attended to the women at delivery. The weights of the babies and the placentas were measured to the nearest 10 g. The infants' body length and head circumference were measured to the nearest 0.1 cm. Women who did not come to the study clinic for their monthly appointments were visited at home when possible and were asked to come to the clinic if their condition allowed.

STUDY OUTCOMES

The primary outcomes were low birth weight (<2500 g), preterm delivery (before 37 weeks of gestation), and fetal death. Secondary outcomes included a birth weight below 2000 g, extremely preterm delivery (before 34 weeks), a size at birth that was small for gestational age (defined as a birth weight below the 10th percentile for gestational age, according to the standards of Brenner et al.[18]), and fetal death and death in the first 6 weeks of life. As in other studies of small-for-gestational-age infants,[13] we used U.S. standards, which are considered to provide a better reflection of growth potential unimpeded by nutritional deprivation than are local norms and thus to provide a reasonable "reference" population. Other secondary outcomes included the following continuous variables: birth weight, length, head circumference, gestational age, and placental weight; risk of cesarean section; maternal mortality, including deaths up to 6 weeks post partum; hematologic status, assessed on the basis of both continuous hemoglobin levels and two categorical definitions of anemia (hemoglobin level <11 g per deciliter and <8.5 g per deciliter); and immune status, assessed on the basis of both continuous CD4+, CD8+, and CD3+ cell counts and categorical counts reflecting the baseline median values as cutoff points (CD4+ count, <775 per cubic millimeter; CD8+ count, <480 per cubic millimeter; and CD3+ count, <1350 per cubic millimeter).

STATISTICAL ANALYSIS

We calculated that we would need to enroll 6000 women in order to examine the effects of the vitamin supplements on the primary outcomes. This calculation was based on the following assumed risks in the placebo group (obtained from pilot data in the same setting): fetal death, 8.8% of pregnancies; low birth weight, 17.6%; and preterm births, 22.6%. Assuming a 10% loss to follow-up, this sample size provided a statistical power of more than 90% to detect protective effects of vitamin supplementation that would be equivalent to at least a 30% reduction in the rates of low birth weight and prematurity and a power of more than 80% to detect at least a 25% reduction in the risk of fetal death. The sample size was later increased to 8468 to increase the power because the observed rates of these outcomes were lower than anticipated. (This increase also permitted the enrollment of 2400 women who would undergo a second round of random assignments to the same two regimens 6 weeks post partum so that we could examine the effects of postnatal multivitamin supplementation on infant health — a separate analysis that is not reported here.)

Treatment effects were assessed by means of an intention-to-treat analysis. For outcomes for children, generalized estimating equations[19] with a compound symmetry working correlation matrix were used to account for correlations due to twinning in the analysis of infant outcomes (155 pairs of twins and 1 set of triplets). Binary end points were assessed with the use of the log link and binomial variance function, and continuous end points were assessed with the use of the identity link and the gaussian variance function.[20] To assess the statistical significance of treatment effects, P values were obtained from the robust score test. To assess the statistical significance of the treatment effects for end points for women, the chi-square test, or Fisher's exact test when warranted, was used for binary variables, and the Wilcoxon rank-sum test was used for continuous variables.[21] A data safety and monitoring board met six times during the study and reviewed the results with regard to efficacy and the safety end points. The protocol called for the use of the Peto

stopping boundary with a nominal P value of 0.001 for early discontinuation.[22]

RESULTS

Of the 8468 women who were enrolled, 40 were not eligible for the study. Among the remaining 8428 women, data on birth outcomes were available for 8379 (99.4%); 6 women died before delivery, and the other 43 were lost to follow-up by the time of delivery (Fig. 1). Of 8379 women with known birth outcomes (miscarriage, stillbirth, or live birth [with a baby born with any evidence of life, such as breathing or heartbeat, considered to be liveborn]), 8137 gave birth to live babies and were eligible for the analyses of birth weight and prematurity outcomes. In this group of women, a birth weight was not recorded for 271 babies (3.3%) because the birth occurred at home or at another medical facility.

The study groups were similar with respect to baseline characteristics (Table 1). The mean (±SD) interval between randomization and delivery was 4.1±1.0 months, and the mean interval between randomization and 6 weeks post partum was 5.6± 1.0 months. These intervals did not differ significantly between the two groups. The average compliance rate (calculated as the number of tablets that were absent from the returned bottles divided by the total number of tablets the participant should have taken) was 88% (median, 96%) for the period from randomization to the time of delivery and 80% (median, 86%) for the period from randomization to 6 weeks post partum. There was no significant difference in compliance between the treatment groups for either period (P=0.57 and P=0.20, respectively).

The risk of low birth weight was 9.4% in the placebo group, which was substantially lower than the 13% rate reported in the general population.[1] Low birth weight was significantly less common in the multivitamin group than in the placebo group (7.8% vs. 9.4%; relative risk, 0.82; 95% confidence interval [CI], 0.70 to 0.95; P=0.01) (Table 2). The mean birth weight was significantly but modestly higher in the multivitamin group than in the placebo group (mean difference between the groups, 67 g; P<0.001).

Multivitamin supplementation had no significant effects on the risk of preterm birth (Table 2) or on the risk of fetal death (4.3% in the multivitamin group and 5.0% in the placebo group; relative risk, 0.87; 95% CI, 0.72 to 1.05; P=0.15) (Table 3). The risk of a birth size that was small for gestational age was reduced by 23% in the multivitamin group (P<0.001) (Table 2).

We reexamined the effects of supplementation among singleton births. As compared with placebo, multivitamins reduced the risks of low birth weight overall (relative risk, 0.79; 95% CI, 0.66 to 0.93; P=0.006) and also among term births (relative risk, 0.76; 95% CI, 0.60 to 0.96; P=0.02). Among all singleton births, the relative risks of birth before 37 weeks' gestation and before 34 weeks' gestation were 0.86 (95% CI, 0.71 to 1.05; P=0.14) and 0.82 (95% CI, 0.64 to 1.05; P=0.12), respectively.

Among all the women, 8.4% in the multivitamin group and 7.3% in the placebo group underwent cesarean section (relative risk, 1.15; 95% CI, 0.99 to 1.33; P=0.06). Multivitamins had no significant effect on the risk of maternal death (P= 0.27). Maternal anemia was less likely in the multivitamin group than in the placebo group, and mean hemoglobin levels and CD4+ cell counts were significantly higher among women assigned to receive multivitamins (P<0.001 for both comparisons), but the absolute differences between the groups were small (Table 4).

DISCUSSION

HIV-negative Tanzanian women who received prenatal supplementation with vitamin B complex and vitamins C and E did not have significantly reduced risks of prematurity and fetal death, but they did have significantly reduced risks of low birth weight. Multivitamins also reduced the risk of a birth size that was small for gestational age and resulted in significant albeit modest improvements in hemoglobin levels and CD4+ cell counts among mothers 6 weeks after delivery.

We previously reported that the same multivitamin regimen improved outcomes among HIV-infected women enrolled in a similarly designed study in Tanzania.[9] In the present study, which involved HIV-negative women, the magnitude of the benefit was smaller. The risks of low birth weight and a birth size that was small for gestational age were reduced by 18% and 23%, respectively, among HIV-negative women, as compared with corresponding reductions of 44% and 43% among HIV-infected women.

Multivitamins, including B vitamins and antioxidant vitamins C and E, may lead to better birth outcomes in several ways. By enhancing maternal

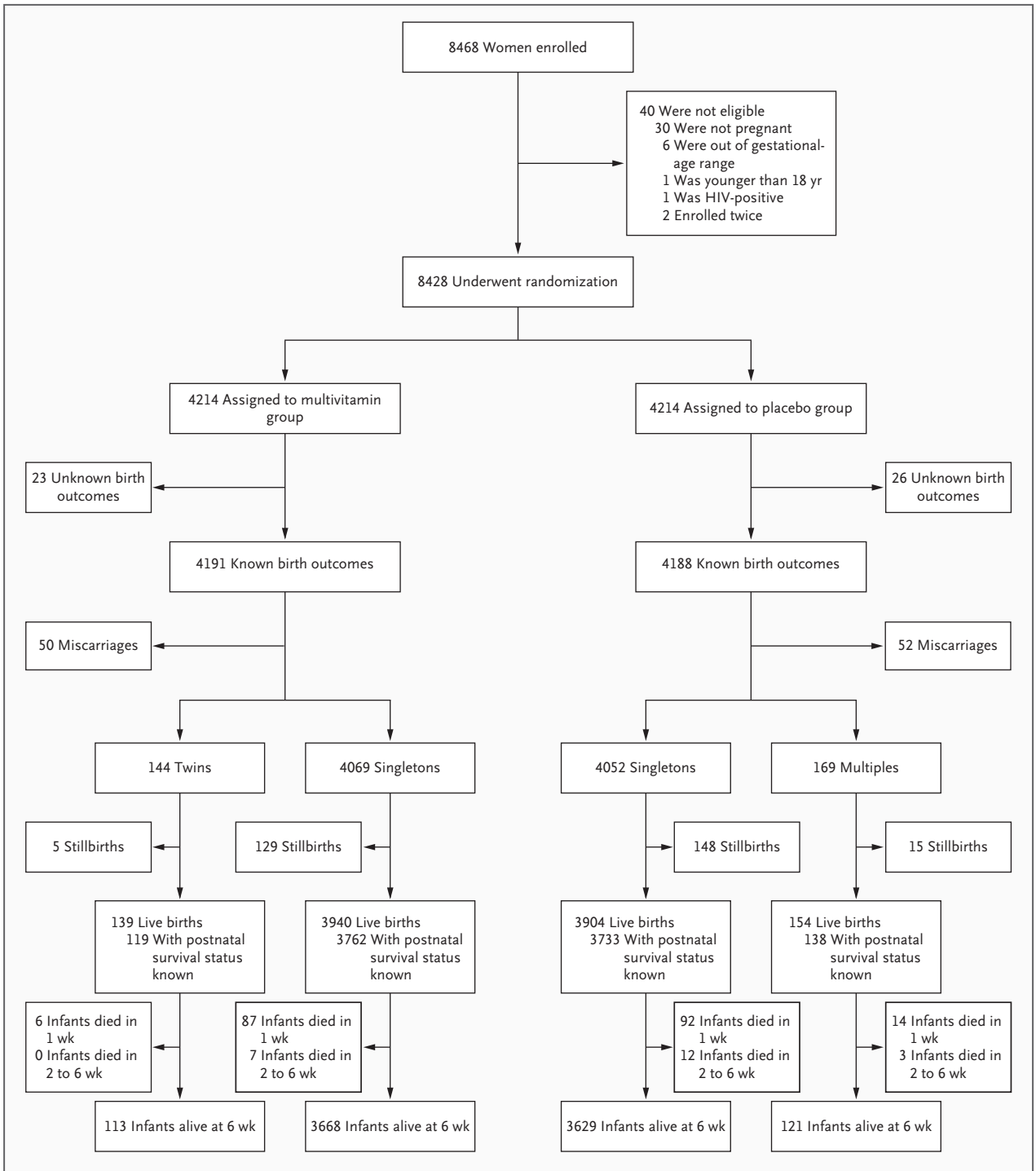

Figure 1. Study Enrollment, Randomization, and Pregnancy Outcomes.

nutritional status and immunity during pregnancy, multivitamins may reduce the risk of intrauterine infections. However, we were not able to examine this hypothesis directly. In observational studies, positive associations were reported between maternal vitamin status and birth outcomes.[23-26] Better birth outcomes may also occur by means of improvements in maternal hematologic status. Low hemoglobin levels are associated with increased risks of adverse pregnancy outcomes, in-

Table 1. Baseline Characteristics of Women in the Multivitamin and Placebo Groups.*

Characteristic	Multivitamin Group (N=4214)	Placebo Group (N=4214)
Gestational age of fetus (wk)	21.3±3.5	21.3±3.5
Maternal age (yr)	25.2±5.1	25.1±5.1
Education (%)†		
0–4 yr	11.6	11.4
5–7 yr	65.9	67.2
8–11 yr	17.3	16.4
≥12 yr	5.2	5.0
Parity (%)‡		
0 (primigravida)	45.5	45.1
1	27.5	27.9
2	14.6	15.0
≥3	12.4	12.0
Body-mass index (%)§		
<22.0	26.3	26.9
22.0–24.9	34.6	35.1
25.0–29.9	30.0	28.2
≥30.0	9.1	9.8
Hemoglobin (%)¶		
<8.5 g/dl	11.9	12.1
8.5–10.9 g/dl	55.9	54.9
≥11.0 g/dl	32.2	33.0
T-cell counts‖		
CD4+ count (cells/mm^3)	807±253	804±263
CD4+ count <775 cells/mm^3 (%)	50.0	51.3
CD3+ count <1350 cells/mm^3 (%)	50.9	50.1
CD8+ count <480 cells/mm^3 (%)	48.7	49.2

* Plus–minus values are means ±SD. There were no significant differences between the multivitamin and placebo groups (P≥0.05).
† Information regarding education was not available for 38 women (0.5%).
‡ Information regarding parity was not available for 45 women (0.5%).
§ The body-mass index is the weight in kilograms divided by the square of the height in meters. The baseline body-mass index was not available for 1034 women (12.3%).
¶ Baseline hemoglobin measurements were not available for 1182 women (14.0%).
‖ Baseline T-cell counts (CD4+, CD8+, and CD3+) were not available for 5598 women (66.5%).

cluding low birth weight.[27] In our previous trial, supplementation with vitamin B complex and vitamins C and E significantly increased the mean hemoglobin level in HIV-positive women at 6 weeks post partum (mean increase, 0.6 g per deciliter),[13] as compared with an increase of 0.2 g per deciliter in the HIV-negative women in the current study. Although the small increase in the HIV-negative women may not be important on an individual level, a small shift of the population distribution toward higher hemoglobin levels may be beneficial from the public health perspective. Vitamin C and riboflavin improve the intestinal absorption of iron. Riboflavin is also necessary for synthesis of the globin component of hemoglobin.[28]

Our findings differ from those of two placebo-controlled trials among presumably HIV-negative pregnant women from Sarlahi, Nepal,[9] and Mexico,[10] which showed no significant effects of multiple micronutrient supplements on birth weight and other pregnancy outcomes. In both trials, the supplement included doses of micronutrients containing the RDA. In a placebo-controlled trial in Janakpur, Nepal, multiple micronutrients containing the RDA resulted in a significant mean difference in birth weight of 77 g and a reduction of 25% in the risk of low birth weight, as compared with placebo; this trial did not show a significant effect of vitamin supplementation on the risk of preterm birth.[11] In a trial in Guinea-Bissau, which compared supplements containing one or two times the RDA of micronutrients with placebo,[29] the incidence of low birth weight was significantly higher among infants of mothers who received placebo than among infants of mothers who received supplements containing twice the RDA (13.6% vs. 10.0%; mean difference in birth weight, 95 g) but was not significantly different from the incidence among infants of mothers who received supplements containing the RDA (low birth weight, 12.0%; mean difference in birth weight between this group and the placebo group, 53 g; P=0.009 for linear trend in birth weight).

The efficacy of supplements that include the RDA may vary in developing countries. In our previous study involving HIV-positive Tanzanian women[13] and in the current study involving HIV-negative Tanzanian women, the supplement contained twice the RDA of vitamin E and 6 to 10 times the RDAs for several B vitamins and vitamin C. HIV-infected persons are likely to require an increased vitamin intake to maintain an adequate nutritional status.[30] Given that the RDA is the level recommended for healthy women in North America, even in the absence of HIV infection, this level of supplementation may be inadequate to meet the requirements of pregnant women in many developing countries because of the

Table 2. Birth Outcomes.

End Point*	No. of Women	No. of Infants	Multivitamin Group	Placebo Group	Difference or Relative Risk	P Value
Birth weight — g	7732	7866				
Mean (95% CI)			3148 (3132 to 3165)	3083 (3067 to 3099)	67 (43 to 89)	<0.001
<2500 g — no. (%)			306 (7.8)	368 (9.4)	0.82 (0.70 to 0.95)	0.01
<2000 g — no. (%)			85 (2.2)	109 (2.8)	0.75 (0.56 to 1.02)	0.06
Gestational age — wk	7996					
Mean (95% CI)			39.5 (39.4 to 39.6)	39.4 (39.3 to 39.5)	0.2 (0.0 to 0.3)	0.02
Preterm birth — no. (%)	7996					
<37 wk			676 (16.9)	666 (16.7)	1.01 (0.91 to 1.11)	0.87
<34 wk			196 (4.9)	222 (5.6)	0.88 (0.73 to 1.06)	0.17
Low birth weight and preterm birth — no. (%)	7732	7866	160 (4.1)	176 (4.5)	0.88 (0.71 to 1.10)	0.27
Low birth weight and term birth — no. (%)	6437	6516	146 (4.5)	192 (5.9)	0.76 (0.61 to 0.95)	0.02
Small for gestational age — no. (%)†	7518	7650	407 (10.7)	523 (13.6)	0.77 (0.68 to 0.87)	<0.001
Length — cm	5540	5640				
Mean (95% CI)			47.5 (47.3 to 47.7)	47.3 (47.1 to 47.5)	0.2 (−0.1 to 0.5)	0.28
Head circumference — cm	6611	6731				
Mean (95% CI)			34.4 (34.3 to 34.5)	34.3 (34.2 to 34.4)	0.1 (0.0 to 0.2)	0.17
Placental weight — g	6722	6746				<0.001
Mean (95% CI)			507 (503 to 510)	498 (495 to 501)	9 (4 to 14)	
Cesarean section — no. (%)	8379		353 (8.4)	307 (7.3)	1.15 (0.99 to 1.33)	0.06

* Gestational age at birth, preterm births, and cesarean sections were considered to be outcomes for women.
† Small for gestational age was defined as a birth weight below the 10th percentile for gestational age. The analysis of this end point was restricted to births at 21 to 44 weeks of gestation.

higher burden of undernutrition and parasitic infections in these countries.

In an analysis of pooled data from the two Nepalese trials, perinatal mortality was paradoxically increased with multivitamin use.[12] The authors suggested that higher birth weight, at least among short and chronically undernourished South Asian women, could lead to difficulty in labor, presumably because of cephalopelvic disproportion, with associated perinatal mortality. The trial in Mexico did not show an adverse effect of supplementation.[10] Fetal mortality was significantly reduced (by 39%) with supplementation in our previous study of HIV-positive Tanzanian women.[13] In the current study, supplementation had no significant effect on fetal mortality; the same was true in the study in Guinea-Bissau.[29] In both the current study and the study in Zimbabwe,[31] the risks of cesarean section did not differ significantly between the multivitamin and placebo groups. Thus, the availability of standard antenatal and obstetrical care that provides for early identification and management of conditions associated with obstructed labor may mitigate concerns about the potentially adverse effects of micronutrient supplements; such care was provided in the African trials that were carried out in large urban centers.

In our current study, the rate of low birth weight in the placebo group was substantially lower than previously reported rates in the general population. This low rate may reflect the high standard of prenatal care provided according to national and World Health Organization guidelines. Even so, multivitamin supplementation had beneficial effects on some pregnancy outcomes. It is not clear whether the effects of supplementation would be different in populations of women

Table 3. Fetal Loss, Miscarriage, Stillbirths, and Infant Deaths.*

Outcome	Time of Death	No. of Women	No. of Infants	Multivitamin Group	Placebo Group	Relative Risk (95% CI)	P Value
				no. (%)			
Fetal loss	Any time before delivery	8379	8536	184 (4.3)	215 (5.0)	0.87 (0.72–1.05)	0.15
Miscarriage	Before 28 weeks' gestation	8379		50 (1.2)	52 (1.2)	0.96 (0.65–1.41)	0.84
Stillbirth	Between 28 weeks' gestation and delivery	8277	8434	134 (3.2)	163 (3.9)	0.84 (0.67–1.05)	0.13
Death							
Perinatal	Between 28 weeks' gestation and 1 week after delivery	7919	8048	227 (5.7)	268 (6.6)	0.88 (0.74–1.04)	0.13
Postnatal	During the first 6 weeks after delivery	7638	7751	100 (2.6)	120 (3.1)	0.86 (0.66–1.13)	0.28
Perinatal or postnatal	Between 28 weeks' gestation and 6 weeks after delivery	7919	8048	234 (5.8)	283 (7.0)	0.86 (0.72–1.02)	0.08
Fetal, perinatal, or postnatal	Any time before delivery or during first 6 weeks after delivery	8021	8150	284 (7.0)	335 (8.2)	0.88 (0.75–1.02)	0.09

* Numbers and percentages of infants are shown for all outcomes except miscarriage, for which numbers and percentages of women are shown, since miscarriage was considered to be an outcome for women.

Table 4. Hemoglobin and T-Cell Counts among Women 6 Weeks after Delivery.

End Point	No. of Women	Multivitamin Group	Placebo Group	Difference or Relative Risk (95% CI)*	P Value
Hemoglobin	6169				
Mean (95% CI) — g/dl		12.1 (12.1 to 12.2)	11.9 (11.9 to 12.0)	0.2 (0.1 to 0.3)	<0.001
<8.5 g/dl — no. (%)		87 (2.8)	104 (3.4)	0.84 (0.63 to 1.11)	0.21
<11 g/dl — no. (%)		593 (19.2)	671 (21.8)	0.88 (0.80 to 0.97)	0.01
CD4+	3017				
Mean (95% CI) — cells/mm^3		924 (909 to 939)	888 (874 to 902)	36 (15 to 57)	<0.001
CD4+ <775 cells/mm^3 — no. (%)		466 (31.0)	577 (38.1)	0.81 (0.74 to 0.90)	<0.001
CD8+	3017				
Mean (95% CI) — cells/mm^3		654 (640 to 668)	640 (626 to 654)	15 (−5 to 34)	0.14
CD8+ <480 cells/mm^3 — no. (%)		424 (28.2)	469 (31.0)	0.91 (0.82 to 1.02)	0.10
CD3+	3017				
Mean (95% CI) — cells/mm^3		1669 (1643 to 1695)	1614 (1588 to 1640)	55 (18 to 92)	0.003
CD3+ <1350 cells/mm^3 — no. (%)		414 (27.5)	510 (33.7)	0.82 (0.73 to 0.91)	<0.001

* Mean differences are shown for continuous variables, and relative risks for categorical variables.

for whom prenatal care is less available. Future trials could assess the effects of varying doses and the addition of other nutrients not included in our regimen.

In conclusion, prenatal multivitamin supplementation significantly reduced the risks of low birth weight and a birth size that was small for gestational age, but it had no significant effects on the risks of prematurity or fetal death. In light of these benefits and the low cost of the supplements, multivitamins should be considered for all pregnant women. Many developing countries have a system for providing prenatal iron and folate supplements; the supplements are produced

in bulk by the United Nations Children's Fund (UNICEF) at an estimated cost of less than $1 per person for the duration of pregnancy.[32] The increase in cost of incorporating the RDA of additional nutrients is conservatively estimated to be about 20%,[32] and scaling up prenatal multiple micronutrient supplementation could be a highly cost-effective approach to improving birth outcomes among pregnant women in developing countries.

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