

Multivitamin Supplementation of HIV-Positive Women during Pregnancy Reduces Hypertension¹

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ABSTRACT Hypertension during pregnancy increases fetal growth retardation, preterm deliveries, and perinatal deaths, and yet its causes remain unclear. In HIV-infected women, preterm birth additionally increases the risk of HIV transmission to the infant. Oxidative stress and endothelial cell dysfunction of the placenta have been implicated in the development of hypertension during pregnancy. Vitamin intake can reduce oxidative stress and improve endothelial function. We therefore evaluated the effect of multivitamin (20 mg thiamine, 20 mg riboflavin, 25 mg B-6, 50 μ g B-12, 500 mg C, 30 mg E, and 0.8 mg folic acid) and vitamin A supplements (30 mg β -carotene plus 5000 IU preformed vitamin A) in relation to hypertension during pregnancy (systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg at any time during pregnancy). In a double-blind, placebo-controlled, randomized, clinical trial, conducted among 1078 HIV-positive pregnant Tanzanian women, those who received multivitamins were 38% less likely to develop hypertension during pregnancy than those who did not [relative risk (RR) = 0.62, 95% CI 0.40–0.94, P = 0.03]. There was no overall effect of vitamin A on hypertension during pregnancy (RR = 1.00, 95% CI 0.66–1.51, P = 0.98). Hypertension during pregnancy was more likely in women with high baseline systolic blood pressure ($>$ 120 vs. \leq 120 mm Hg) (RR = 6.02, 95% CI 2.59–13.97, P < 0.001), and those with higher mid-upper arm circumference (RR = 1.12, 95% CI 1.04–1.19, P = 0.002). Taking multivitamins containing vitamins B, C, and E during pregnancy may be an inexpensive and effective strategy to improve the health of the mother and baby. *J. Nutr.* 135: 1776–1781, 2005.

KEY WORDS: • multivitamins • hypertension during pregnancy • randomized controlled trial

Hypertension during pregnancy increases fetal growth retardation, preterm deliveries, and perinatal deaths, and yet its causes remain unclear (1). Even though improvements in postnatal care reduced perinatal deaths rates in developed countries, preeclampsia rates remained constant at between 3 and 10% of all births (2), and preterm birth rates have increased (3). The worldwide prevalence of hypertensive disorders during pregnancy is 15% (4). In developing countries, \sim 25% of newborns have growth retardation (5), and perinatal mortality ranges from 150 to 400/1000 live births (6); 10% of perinatal deaths in Africa are related to hypertension during pregnancy (7). In HIV-infected women, preterm birth additionally increases the risk of HIV transmission to the infant (8).

There are few interventions known to prevent hypertension during pregnancy (9). Aspirin was shown to reduce the

risk of preeclampsia in women with underlying risk factors (10). The results of calcium supplementation to prevent hypertension during pregnancy were inconsistent (9). Large doses of vitamin C (1000 mg/d) and vitamin E (400 IU/d) given to high-risk British women reduced preeclampsia but there was no effect on gestational hypertension (11). Folate alone or in combination with iron did not protect against hypertension during pregnancy (9). Other B vitamins, carotenoids, or multivitamin supplements have not been evaluated in relation to preeclampsia or other hypertensive disorders during pregnancy (9).

Oxidative stress and endothelial cell dysfunction of the placenta have been implicated in the development of clinical preeclampsia (2). Low serum antioxidant levels were associated with increased oxidative stress and endothelial cell dysfunction (12); high serum homocysteine was related to increased risk of preeclampsia, preterm birth, and low birthweight (13). B vitamin intake reduces serum homocysteine (14) and improves endothelial function (15). Dietary antioxidants quench reactive oxygen species, reduce oxidative stress, and improve endothelial function (16). It is plausible, therefore, that multivitamin supplements may reduce the risk

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of hypertension during pregnancy, particularly in populations at risk of nutritional deficiencies. Vitamin supplementation is affordable, safe, and can be easily implemented. We enrolled 1078 HIV-infected pregnant Tanzanian women in a double-blind, factorial, randomized, placebo-controlled trial to examine the effect of prenatal multivitamin (vitamins B, C, and E) and vitamin A supplements on HIV mother-to-child transmission and HIV progression. The results of these studies were reported earlier (17,18). In this investigation, we examined the relation between multivitamin and vitamin A supplementation and hypertension in pregnant women.

SUBJECTS AND METHODS

Study population. Recruitment into this randomized, controlled trial evaluating the effects of vitamin supplements and pregnancy outcomes in HIV-1 infected women in Tanzania began in April 1995 and continued for 2 y (17). The primary aims were to evaluate vitamin supplementation in relation to adverse birth outcomes and maternal-to-child HIV transmission (17,19). Evaluating hypertension during pregnancy was a secondary aim.

For these analyses, we followed up women from recruitment to 3 mo postpartum, consistent with other studies evaluating maternal outcomes (20). Pregnant women between 12 and 27 wk gestation who were HIV-1 infected without WHO-defined Stage IV disease (21), resident of Dar-es-Salaam, intending to remain in the city for the duration of the pregnancy and 1 y thereafter were eligible (details are described elsewhere) (17).

We included women for whom we had at least 1 blood pressure assessment at baseline and 1 between randomization and 90 d postpartum. Of the 1078 women who were randomized in the trial, 1073 had baseline blood pressure measurements and 41 had hypertension; 999 had follow-up visits leaving 955 women in this analysis. The study protocol was approved by the respective ethics committees of Muhimbili University of Health Sciences, Dar-es-Salaam, Tanzania and Harvard School of Public Health, Boston, MA. We obtained written consent from all participants.

Intervention. Randomization followed a 2 × 2 factorial design. Women in group A³ (n = 238) were given vitamin A (30 mg

β-carotene plus 5000 IU preformed vitamin A); those in group MV (n = 243) were given multivitamins excluding vitamin A (20 mg thiamine, 20 mg riboflavin, 25 mg B-6, 50 μg B-12, 500 mg C, 30 mg E, and 0.8 mg folic acid); those in group MV+A (n = 242) were given all vitamins, and those in group P (n = 232) were given placebo. All regimen tablets were similar in appearance, identically packaged and labeled; the participant, dispenser, and study physicians were unaware of their contents. All women were given 400 mg ferrous sulfate, 5 mg folate, and 500 mg chloroquine phosphate. At delivery, all women taking vitamin A were administered a single oral dose of 200,000 IU vitamin A; the others were given an extra dose of placebo.

At every visit, we exchanged old regimen bottles containing any leftover pills for new bottles. To check compliance, we subtracted the number of pills returned from the total number administered to calculate the percentage of pills taken and compared plasma vitamin A levels at baseline to that at delivery for a subgroup of 100 women.

Outcome assessment. A woman was considered hypertensive if her systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥ 90 mm Hg at any time during pregnancy. The nurse measured the blood pressure using a mercury sphygmomanometer with the woman sitting rested on a chair, and recorded single values for systolic and diastolic blood pressure. Measurements were made at least monthly at prenatal visits, at delivery, and at postnatal visits.

Data collections for other covariates. Information on sociodemographic characteristics was collected at baseline and all routine laboratory tests were conducted as described elsewhere (19). A study physician examined the patient; a nurse obtained the history and measured height, weight, and mid-upper arm circumference at baseline and every subsequent month. Gestational age was determined by the physician using the date of the last menstrual period.

Statistical analysis. In the analysis for treatment effect of vitamins on hypertension during pregnancy, we excluded women with hypertension at the time of randomization, and considered the first event of hypertension between randomization and 3 mo postpartum. We calculated person time from randomization to the first diagnosis of hypertension during pregnancy, loss to follow-up, or 90 d postpartum, whichever came first. In intention-to-treat analyses, we used the Kaplan-Meier estimator to obtain cumulative rates and the Cox proportional hazards model to estimate relative risks (RR) and the 95% CI for the effect of vitamins on hypertension. The α level was set at 5%. We analyzed the main effects of vitamin A, multivitamins, and their interactions. We explored effect modification by CD4 cell count, lymphocyte count, erythrocyte sedimentation rate (ESR), hemoglobin, age, baseline BMI, history of diabetes, nulliparity, liter-

TABLE 1

Baseline characteristics of participants by intervention group¹

	Multivitamins ²	Placebo ³	Vitamin A	Placebo ⁴
n	485	470	480	475
Age, y	24.7 ± 4.7	24.7 ± 4.8	24.7 ± 4.7	24.7 ± 4.7
Systolic blood pressure, mm Hg	106 ± 10	106 ± 10	106 ± 10	106 ± 10
Diastolic blood pressure, mm Hg	66 ± 8	66 ± 8	66 ± 8	66 ± 8
BMI, kg/m ²	23.4 ± 3.1	23.1 ± 3.3	23.2 ± 3.2	23.2 ± 3.2
Mid-upper arm circumference, cm	25.6 ± 2.7	25.5 ± 2.9	25.5 ± 2.8	25.6 ± 2.9
Height, cm	156.7 ± 5.7	156.6 ± 6.1	156.7 ± 6.0	156.7 ± 5.7
Gestational age, wk	20.4 ± 3.2	20.3 ± 3.5	20.2 ± 3.4	20.5 ± 3.2
Hemoglobin, g/L	94 ± 16	95 ± 17	94 ± 17	95 ± 17
Lymphocyte count, cells/mm ³	1869 ± 843	1839 ± 707	1847 ± 778	1860 ± 779
Erythrocyte sedimentation rate, mm/h	58 ± 35	60 ± 37	58 ± 36	61 ± 37
CD4 cell count, cells/mm ³	422 ± 202	411 ± 209	412 ± 204	421 ± 207
CD8 cell count, cells/mm ³	747 ± 326	744 ± 317	749 ± 316	740 ± 328
Plasma vitamin A, mmol/L	0.86 ± 0.32	0.85 ± 0.35	0.84 ± 0.31	0.86 ± 0.36
Plasma vitamin E, mmol/L	0.23 ± 0.07	0.23 ± 0.07	0.23 ± 0.07	0.23 ± 0.07

¹ Values are means ± SD. The multivitamin and vitamin A groups did not differ from their respective placebo groups for any of the variables.

² Vitamins B, C, and E.

³ This placebo group includes women in group P and group A.

⁴ This placebo group includes women in group P and group MV.

acy level, and plasma vitamins A and E by comparing full and reduced Cox models using the likelihood ratio test. All of the analyses in Figure 1, and Tables 2 and 3 were unadjusted for any covariates. To assess the predictors of hypertension during pregnancy, we included all potential predictors in a forward stepwise Cox proportional hazards model with entry and staying criteria for the variables set at 0.20.

RESULTS

Of the 955 HIV-positive pregnant women in this analysis, 485 were administered multivitamins and 470 were not. Women in the 4 intervention groups, MV, A, MV+A, and P, had similar baseline characteristics (Table 1). Most women took the medication they were administered; the mean compliance with the regimen was 91% (median 96%) from the time of randomization to delivery for all groups (17). The plasma concentrations of vitamin A among women who did

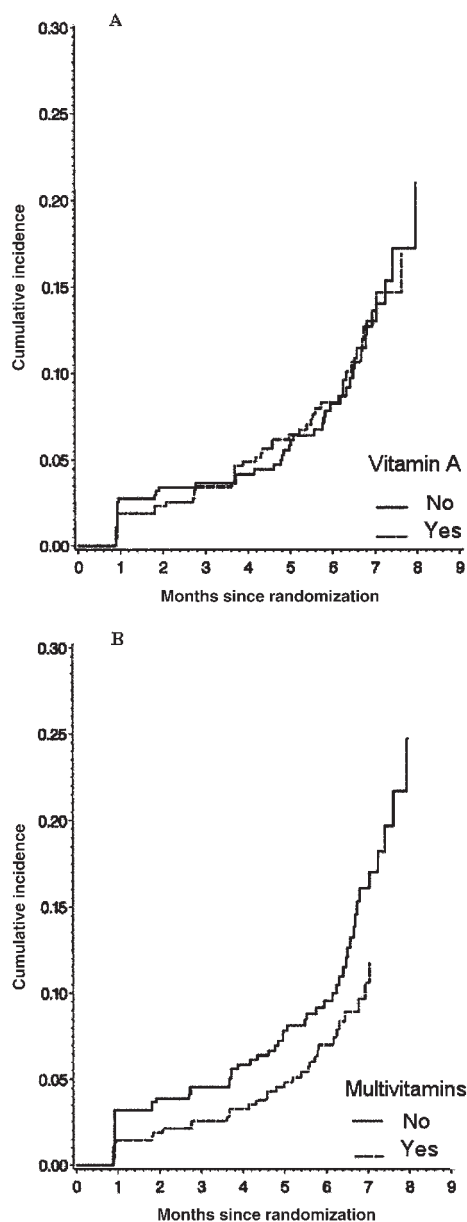


FIGURE 1 Kaplan-Meier graph comparing time to first episode of hypertension by vitamin A (panel A) and multivitamin use (panel B) in pregnant, HIV-positive women.

TABLE 2

Multivitamin and vitamin A intake and development of hypertension during pregnancy in HIV-positive women¹

	Hypertension cases	Total ¹	Person-mo	Incidence/10 ³ person-mo
<i>n</i>				
Multivitamin intake				
Yes	35	485	2682	130
No	54	470	2528	214
RR (95% CI) ²	0.62 (0.40–0.94)			
<i>P</i> -value	0.03			
Vitamin A intake				
Yes	45	480	2637	171
No	44	475	2574	171
RR	1.00 (0.66–1.51)			
<i>P</i> -value	0.98			

¹ Number of women in group.

² RR (hazard ratio) and 95% CI from unadjusted Cox proportional hazards model, *P*-value for interaction between multivitamins and vitamin A is 0.97.

and did not receive vitamin A were similar at baseline (0.84 and 0.86 mmol/L, respectively, *P* = 0.67), but differed at the end of the study (0.98 and 0.80 mmol/L, respectively, *P* = 0.01) (17).

Of 995 HIV-positive pregnant women, 130 (13%) had hypertension; of these, 41 were hypertensive at the time of randomization. There were 89 incident hypertension cases after randomization over 5211 person-mo of follow up (171 cases/10,000 person-mo).

Women who received multivitamins were less likely to develop incident hypertension during pregnancy than those who did not (Fig. 1). The difference between the 2 groups was apparent shortly after the first month following randomization and remained until the end of the study. Overall, multivitamins reduced the hypertension risk during pregnancy by 38% (RR = 0.62, 95% CI 0.40–0.94, *P* = 0.03) (Table 2). The effect of multivitamins on hypertension during pregnancy remained inverse and significant when we restricted the analyses to cases not detected until delivery, and when we included baseline cases of hypertension and those detected at the first contact after delivery (data not shown).

Vitamin A did not affect hypertension during pregnancy; the Kaplan-Meier graphs of the vitamin A and no vitamin A groups overlapped over the entire course of follow-up (Fig. 1), (RR = 1.00, 95% CI 0.66–1.51, *P* = 0.98) (Table 2).

This study was not designed to evaluate effect modification of the relation between multivitamin intake and hypertension risk; thus, data were sparse in some of the categories. The effect of multivitamins on hypertension during pregnancy did not differ between women who did and did not receive vitamin A (*P*-value for interaction = 0.97). The effect of multivitamins on hypertension was not modified by any of the factors we evaluated (Table 3).

In the analysis of predictors of hypertension during pregnancy, systolic blood pressure at baseline > 120 mm Hg (after excluding women with systolic blood pressure ≥ 140 mm Hg) and mid-upper arm circumference at baseline were related to hypertension risk during pregnancy after adjustment for age. Women with systolic blood pressure > 120 mm Hg at baseline were 6 times more likely to have hypertension during pregnancy than women with systolic blood pressure ≤ 120 mm Hg (RR = 6.02, 95% CI 2.59–13.97, *P* = 0.002). There was a

TABLE 3

The effect of multivitamins on hypertension during pregnancy within strata of potential effect modifiers in HIV-positive women

	Total	Cases	Person-mo ¹	Incidence/10 ² person-mo	RR (95% CI) ³	P-value	P-value for interaction ²
<i>n</i>							
Age, y							
<20	113	6	593	101	1.78 (0.33–9.73)	0.51	0.42
20–29	726	64	3977	161	0.57 (0.34–0.94)	0.03	
≥30	116	19	641	296	0.60 (0.24–1.54)	0.29	
BMI, kg/m ²							
<19	53	2	313	64			
19–24.9	658	53	3612	147	0.57 (0.32–0.99)	0.04	0.53
≥25	223	31	1181	263	0.64 (0.31–1.32)	0.23	
Parity, <i>n</i>							
0	248	25	1281	195	0.81 (0.37–1.78)	0.60	0.32
>0	684	63	3818	165	0.52 (0.31–0.87)	0.01	
Literacy							
Literate	885	86	4842	178	0.62 (0.40–0.96)	0.03	0.80
Illiterate	70	3	369	81	0.47 (0.04–5.17)		
Pregnant with twins							
No	930	88	5090	173	0.62 (0.41–0.95)	0.03	0.40
Yes							
Height <150 cm							
No	856	81	4676	173	0.67 (0.43–1.05)	0.08	0.12
Yes	97	8	528	152	0.16 (0.02–1.28)	0.08	
Systolic BP > 120 mm Hg							
No	939	82	5146	161	0.56 (0.36–0.88)	0.01	0.22
Yes	16	6	65	927	2.74 (0.48–15.30)		
Lymphocytes, cells/mm ³							
<1340	232	23	1304	176	0.52 (0.22–1.24)	0.14	0.59
≥1340	706	65	3815	170	0.68 (0.41–1.11)	0.12	
Hemoglobin, g/L							
<85	258	17	1379	123	0.85 (0.33–2.20)	0.73	0.52
≥85	683	71	3755	189	0.68 (0.41–1.11)	0.12	
ESR, mm/h							
<81	227	21	1188	177	0.87 (0.37–2.06)	0.73	0.52
≥81	642	63	3528	179	0.58 (0.35–0.97)	0.04	
CD4 cells, cells/mm ³							
<350	339	29	1863	156	0.40 (0.18–0.90)	0.03	0.14
≥350	541	50	2961	169	0.84 (0.48–1.47)	0.54	
Plasma vitamin A, mmol/L							
<0.70	223	18	1133	159	0.61 (0.24–1.57)	0.31	0.39
≥0.70	419	41	2383	172	0.37 (0.18–0.73)	0.004	
Plasma vitamin E, mmol/L							
<0.23	309	22	1765	125	0.50 (0.20–1.22)	0.13	0.58
≥0.23	334	38	1755	216	0.36 (0.18–0.72)	0.004	

¹ Note: Numbers of person-mo may not add up to grand totals because of missing data. Rounding may also cause slight discrepancies.

² P-values for interaction from likelihood ratio test.

³ RR (hazard ratio) and 95% CI from unadjusted Cox proportional hazards models.

12% increased risk of hypertension during pregnancy for every centimeter increase in mid-upper arm circumference at baseline (RR = 1.12, 95% CI 1.04–1.19, $P < 0.001$).

DISCUSSION

In our study, multivitamins reduced hypertension risk during pregnancy, whereas vitamin A alone did not among HIV-infected Tanzanian women. This is consistent with our previous finding from this cohort reporting that multivitamins but not vitamin A increased birth weight, and reduced prematurity, fetal loss, and HIV progression in the mother (18). Hypertension during pregnancy increases the risk of intrauterine growth retardation, preterm birth, and perinatal death (1). Hypertension during pregnancy has been hypothesized to affect adverse birth outcomes by reducing placental perfusion and impairing remodeling of placental blood vessels, but the

mechanisms are not clearly understood (1). It is plausible that the improvements in pregnancy outcomes previously detected in this cohort were mediated in part by reduced hypertension in women administered multivitamins.

Dyslipidemia, i.e., increased serum triglycerides, LDL cholesterol, and free fatty acids, precedes preeclampsia, increasing lipid peroxidation, oxidative stress (22), and endothelial dysfunction (23). Oxidative stress is hypothesized to induce endothelial dysfunction of the placental blood vessels (2) and to impair uteroplacental blood flow, increase placental free radical synthesis (24), deplete serum antioxidants (25), and raise preeclampsia risk.

Vitamins C and E can act as scavengers of free radicals (11), decrease oxidative stress, and improve endothelial dysfunction. Habitual vitamin E intake was negatively correlated with diastolic blood pressure among HIV-infected subjects (26). A com-

bination of vitamin C and E supplements reduced preeclampsia by 61% in high-risk women (RR = 0.39, 95% CI 0.17–0.90) (11). It is plausible, therefore, that the antioxidant content of the multivitamin contributed to the reduction in hypertension.

High serum homocysteine was also hypothesized to induce oxidative stress and endothelial dysfunction (27) and is positively associated with preeclampsia risk (28) and adverse pregnancy outcomes (13). Low intakes of vitamins B-6, vitamin B-12, and folate are related to high plasma homocysteine concentration (14). All women in this study received folate and iron, but folate and iron alone were not shown to affect preeclampsia (9). It is possible that the reduction of hypertension risk was through reduction in homocysteine in women who received folate, vitamin B-6, and vitamin B-12.

Carotenoid supplementation has not been evaluated in relation to preeclampsia, but low-dose vitamin A and β -carotene supplementation in Nepal caused a reduction in maternal mortality. Moreover, the proportion of women dying as a result of eclampsia and preeclampsia was similar in the intervention and placebo groups (9). These results suggest that vitamin A and carotenoids probably do not have a direct effect on eclampsia and preeclampsia. The lack of association between vitamin A intake and hypertension during pregnancy in our study is consistent with those findings.

Antiretroviral protease inhibitors induce insulin resistance and dyslipidemia (29), 2 factors associated with eclampsia (1). HIV-positive women administered antiretroviral treatment had higher preeclampsia prevalence than HIV-positive women not given antiretroviral treatment; the latter had a prevalence of preeclampsia similar to that of HIV-negative women (30). The women in our study did not receive antiretroviral treatment; therefore, the hypertension observed in this population could not be attributed to the effects of antiretroviral treatment.

The strongest predictor of hypertension during pregnancy in the current study was modestly elevated blood pressure at baseline, consistent with the literature (24). We observed a positive association between mid-upper arm circumference and the risk of hypertension during pregnancy. We used mid-upper arm circumference instead of BMI as a measure of adiposity because women entered the study at different stages of gestation and we did not have information about their prepregnancy BMIs. Obesity is associated with increased risk of preeclampsia (31) and insulin resistance during pregnancy (32). Hyperinsulinemia is associated with increased blood cholesterol, triglycerides, free fatty acids, and oxidized lipids (32), which might contribute to endothelial dysfunction and increased hypertension risk during pregnancy.

A limitation of this study was that we measured hypertension in a clinical setting using a single recording; this did not follow international guidelines, which recommend 2 readings 4 h apart (33). However, the nurses were trained in measuring blood pressures and followed a defined clinical protocol. Because blood pressure was measured in the same way in all of the women and this was a double-blind study, any misclassification of hypertensive status would most likely be random. This would result in an attenuation of effect, but would not create spurious relations. Another limitation was that we did not have data on proteinuria; thus, we could not classify the cases as eclampsia or preeclampsia. Our definition of hypertension was therefore a composite of preeclampsia, eclampsia, and chronic hypertension. Because it included chronic hypertension (in which blood pressure may be raised for several weeks postpartum), we included women with hypertension at their first postpartum visit because we did not have blood pressure measurements made just before delivery. Confounding is not

likely to contribute to our results because randomization ensured that the comparison groups were similar. In generalizing the results, we must consider that this study was conducted among Tanzanian women with HIV in whom nutritional status was compromised. There is a need to evaluate this relation in HIV-negative women as well.

Prenatal multivitamin intake during pregnancy reduced the incidence of hypertension during pregnancy in this group of HIV-infected women. Taking multivitamins during pregnancy may be an inexpensive and effective strategy to improve the health of the mother and baby.

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