ORIGINAL ARTICLE

Vitamins C and E to Prevent Complications of Pregnancy-Associated Hypertension

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ABSTRACT

BACKGROUND

Oxidative stress has been proposed as a mechanism linking the poor placental perfusion characteristic of preeclampsia with the clinical manifestations of the disorder. We assessed the effects of antioxidant supplementation with vitamins C and E, initiated early in pregnancy, on the risk of serious adverse maternal, fetal, and neonatal outcomes related to pregnancy-associated hypertension.

METHODS

We conducted a multicenter, randomized, double-blind trial involving nulliparous women who were at low risk for preeclampsia. Women were randomly assigned to begin daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E or matching placebo between the 9th and 16th weeks of pregnancy. The primary outcome was severe pregnancy-associated hypertension alone or severe or mild hypertension with elevated liver-enzyme levels, thrombocytopenia, elevated serum creatinine levels, eclamptic seizure, medically indicated preterm birth, fetal-growth restriction, or perinatal death.

RESULTS

A total of 10,154 women underwent randomization. The two groups were similar with respect to baseline characteristics and adherence to the study drug. Outcome data were available for 9969 women. There was no significant difference between the vitamin and placebo groups in the rates of the primary outcome (6.1% and 5.7%, respectively; relative risk in the vitamin group, 1.07; 95% confidence interval [CI], 0.91 to 1.25) or in the rates of preeclampsia (7.2% and 6.7%, respectively; relative risk, 1.07; 95% CI, 0.93 to 1.24). Rates of adverse perinatal outcomes did not differ significantly between the groups.

CONCLUSIONS

Vitamin C and E supplementation initiated in the 9th to 16th week of pregnancy in an unselected cohort of low-risk, nulliparous women did not reduce the rate of adverse maternal or perinatal outcomes related to pregnancy-associated hypertension (ClinicalTrials.gov number, NCT00135707).

Preeclampsia has been considered to be a two-stage disorder. Abnormal placentation or perfusion results in an increased inflammatory response and endothelial dysfunction, which in turn lead to the characteristic maternal syndrome.[1] Oxidative stress is one of several mechanisms that have been proposed to cause manifestations of the disease; it has been suggested that the generation of free radicals in response to reduced placental perfusion may lead to clinical manifestations.[2] Support for this concept is provided by data showing that there are oxidative modifications of proteins,[3,4] lipids,[2,5,6] and DNA[7] in the blood and tissue of women with preeclampsia and their infants, as well as the observation that the concentrations of buffering antioxidants, such as ascorbate, are reduced starting early in pregnancy in women in whom preeclampsia develops later in the pregnancy.[8] Although not all data support this hypothesis,[9] there was enough evidence by the late 1990s to support the performance of a randomized, controlled trial of antioxidant therapy, initiated early in pregnancy, to prevent the clinical signs of preeclampsia.[10] In a study involving 283 women at high risk for preeclampsia, supplementation with vitamins C and E, as compared with placebo, was effective in reducing evidence of endothelial activation; moreover, there was a 60% reduction in the diagnosis of preeclampsia. This study stimulated several groups, including the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Maternal–Fetal Medicine Units (MFMU) Network, to perform larger, randomized trials involving women at high risk and women at low risk for the disorder.[11-14] None of these studies replicated the original positive findings. In contrast with the other studies, our trial was designed to detect a modest effect size in serious outcomes associated with gestational hypertension and preeclampsia among low-risk women, with treatment beginning early in the pregnancy.

METHODS

STUDY POPULATION

We conducted the trial from July 2003 through February 2008 at the 16 clinical centers and the independent data coordinating center of the MFMU Network. Pregnant women who had a singleton fetus with a gestational age of less than 16 weeks 0 days at the time of screening were eligible for inclusion in the study. Gestational age at randomization was between 9 weeks 0 days and 16 weeks 6 days. Women were eligible for inclusion if they had not had a previous pregnancy that lasted beyond 19 weeks 6 days. Gestational age was determined before randomization with the use of a previously described algorithm[15] that took into account the date of the last menstrual period (if reliable information was available) and results of the earliest ultrasound examination. Women were not eligible if they had elevated systolic blood pressure (135 mm Hg or higher), elevated diastolic blood pressure (85 mm Hg or higher), or proteinuria (300 mg of protein or more, as measured in a 24-hour urine sample, or a urine-dipstick result of 1+ or higher for protein), were taking or had taken antihypertensive medication, or were taking more than 150 mg of vitamin C or more than 75 IU of vitamin E daily. Other exclusion criteria were diabetes that was present before the pregnancy, treatment with antiplatelet drugs or nonsteroidal antiinflammatory agents, uterine bleeding within the week before recruitment, uterine malformation, serious medical condition, known fetal anomaly or aneuploidy, in vitro fertilization resulting in the current pregnancy, or abuse of illicit drugs or alcohol.

STUDY DESIGN

Eligible women who were no more than 15 weeks pregnant and who consented to participate in the study were given a supply of placebo and asked to return within 2 weeks. Those who returned, who had taken at least 50% of the placebo that they were supposed to have taken, and who still met the eligibility criteria were randomly assigned to receive capsules containing a combination of 1000 mg of vitamin C (ascorbic acid) and 400 IU of vitamin E (RRR-alpha-tocopherol acetate) or matching placebo (mineral oil). Both the vitamin and placebo capsules were manufactured by Strides, which had no role in the design of the study, the analysis or interpretation of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication. The simple urn method, with stratification according to clinical center, was used by the data coordinating center to create a randomization sequence[16]; boxes containing each participant's supply of capsules were packaged according to this sequence. Neither the participants nor the investigators were aware of the treatment assignments.

Women were instructed to take the study drug each day until they delivered their babies. The study participants returned on a monthly basis to return any unused study drug from the previous month, receive a new supply of the study drug for the coming month, report on side effects, and have their blood pressure and urine protein level (as assessed on dipstick testing) measured. Clinical research staff also obtained data on neonatal and maternal outcomes at delivery.

To determine the primary outcome and the diagnosis of preeclampsia, deidentified medical charts of all women with pregnancy-associated hypertension were reviewed centrally by at least three reviewers who were unaware of the treatment assignments. All data were collected or abstracted by certified research personnel at the clinical centers and uploaded to a database that was managed by an independent data coordinating center, which was responsible for data analysis. The study was approved by the institutional review board at each clinical site and the data coordinating center. All participants provided written informed consent before enrollment.

PRIMARY OUTCOME

The primary outcome was a composite of pregnancy-associated hypertension and serious adverse outcomes in the mother or her fetus or neonate — severe pregnancy-associated hypertension alone or severe or mild pregnancy-associated hypertension with one or more of the following: elevated liver enzyme levels (an aspartate aminotransferase level ≥100 U per liter), thrombocytopenia (a platelet count of <100,000 per cubic millimeter), elevated serum creatinine level (≥1.5 mg per deciliter [132.6 μmol per liter]), eclamptic seizure, an indicated preterm birth before 32 weeks of gestation owing to hypertension-related disorders, a fetus that was small for gestational age (below the 3rd percentile) adjusted for sex and race or ethnic group,[17] fetal death after 20 weeks of gestation, or neonatal death. The diagnosis of hypertension was based on blood-pressure measurements obtained during or after the 20th week of pregnancy, excluding intraoperative blood pressures and intrapartum systolic pressures. Severe pregnancy-associated hypertension was defined as a systolic pressure of 160 mm Hg or more or a diastolic pressure of 110 mm Hg or more on two occasions 2 to 240 hours apart, or a single blood-pressure measurement that was severely elevated and that led to treatment with an antihypertensive medication. Mild pregnancy-associated hypertension was defined as a systolic pressure between 140 and 159 mm Hg or a diastolic pressure between 90 mm and 109 mm Hg on two occasions 2 to 240 hours apart. To be considered part of the primary outcome, an abnormal laboratory value had to be present within 10 days before or anytime after the onset of the pregnancy-associated hypertension.

SECONDARY OUTCOMES

Secondary outcomes included preeclampsia and other maternal and neonatal outcomes. Mild preeclampsia was defined as mild pregnancy-associated hypertension with documentation of proteinuria within 72 hours before or after an elevated blood-pressure measurement. Proteinuria was defined as total protein excretion of 300 mg or more in a 24-hour urine sample or 2+ or higher on dipstick testing, or a protein-to-creatinine ratio of 0.35 or more if a 24-hour urine sample was not available. After the rupture of membranes, only catheterized urine samples were considered in the diagnostic criteria. Severe preeclampsia was defined as preeclampsia with either severe pregnancy-associated hypertension or protein excretion of 5 g or more in a 24-hour urine sample or as mild pregnancy-associated hypertension with oliguria (<500 ml in a 24-hour urine sample), pulmonary edema (confirmed by radiography), or thrombocytopenia (platelet count of <100,000 per cubic millimeter). The HELLP syndrome (hemolysis, elevated liver enzyme levels, and a low platelet count) was considered to be present if pregnancy-associated hypertension occurred with all of the following: a platelet count of less than 100,000 per cubic millimeter, an aspartate aminotransferase level of 100 U per liter or more, and evidence of hemolysis (either a lactate dehydrogenase level ≥600 U per liter or a total bilirubin level ≥1.2 mg per deciliter, or a peripheral-blood smear showing nucleated red cells, schistocytes, or an elevated reticulocyte count).

STATISTICAL ANALYSIS

The expected rate of the primary outcome in the placebo group was estimated from a previous MFMU Network study of low-dose aspirin to prevent preeclampsia in nulliparous women.[18] We esti-

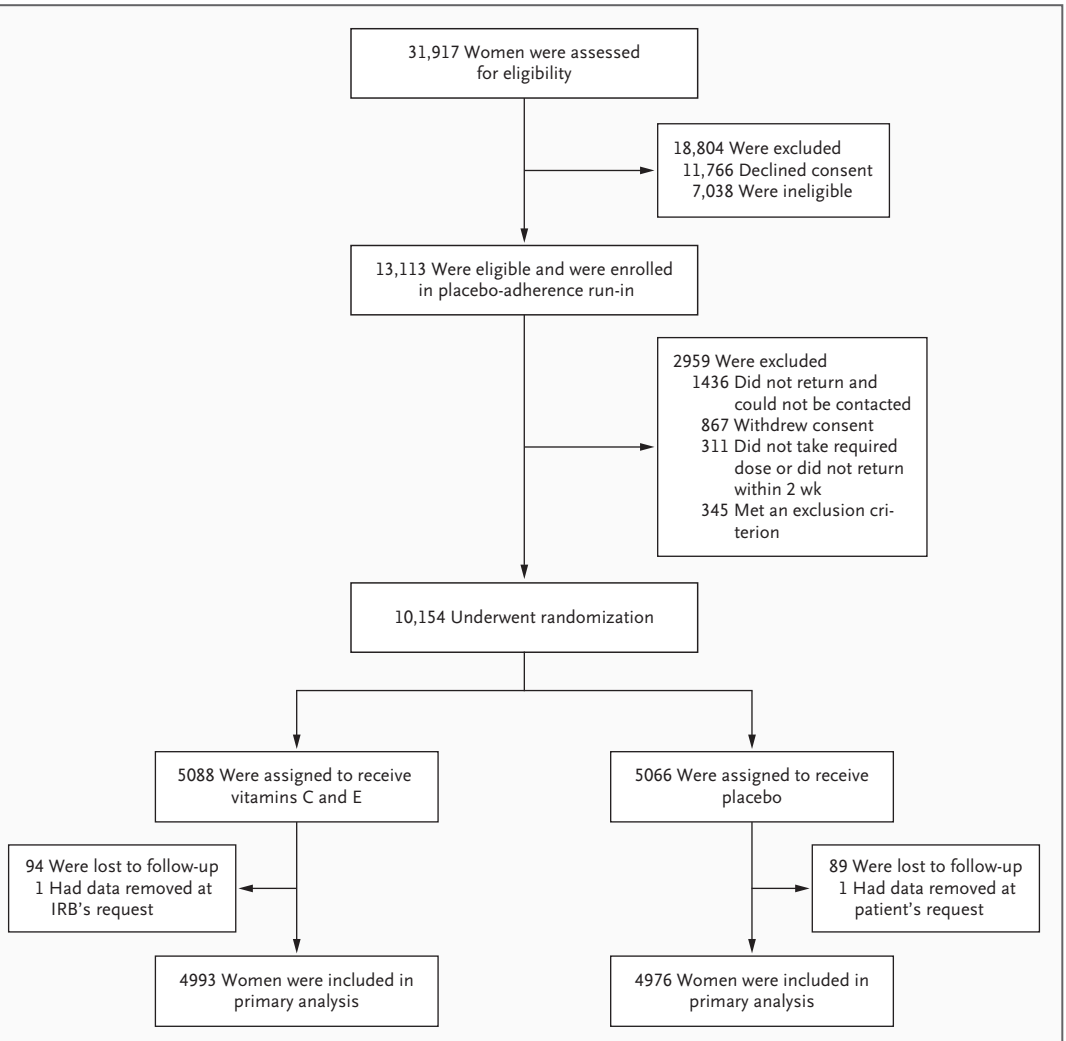

Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.
IRB denotes institutional review board.

mated that with a sample size of 10,000 women, the study would have 90% power to show a 30% reduction in the rate of the primary outcome, from 4% in the placebo group to 2.8% in the vitamin group, with a two-sided type I error rate of 5%.

An independent data and safety monitoring committee monitored the trial and reviewed interim results. A group sequential method was used to characterize the rate at which the type I error was spent; the chosen spending function was the Lan–DeMets generalization of the O'Brien–Fleming boundary.[19] Three interim analyses were performed. In the final analysis of the primary outcome, two-tailed P values of less than 0.045 were considered to indicate statistical significance. However, since the adjustment is minimal, we report 95% confidence intervals.

Data from all women were analyzed according to the group to which they were randomly assigned, regardless of whether they took the study capsules. Continuous variables were compared with the use of the Wilcoxon rank-sum test, and categorical variables with the use of the chi-square test. For all secondary outcomes, nominal P values of less than 0.05 were considered to indicate statistical significance; P values have not been adjusted for multiple comparisons. Unless indicated, all analyses that are presented were prespecified.

Table 1. Baseline Maternal Characteristics.*

Characteristic	Vitamins (N=5087)	Placebo (N=5065)
Age — yr	23.5±5.2	23.5±5.2
Week of pregnancy at randomization	13.4±2.1	13.4±2.1
<13th week of pregnancy at randomization — no. (%)	2227 (43.8)	2203 (43.5)
Race or ethnic group — no. (%)†		
Black	1268 (24.9)	1295 (25.6)
Hispanic	1602 (31.5)	1566 (30.9)
Other	2217 (43.6)	2204 (43.5)
Prepregnancy body-mass index‡	25.4±6.0	25.4±5.9
Smoker — no. (%)	812 (16.0)	781 (15.4)
Educational level — yr	12.8±2.7	12.8±2.7
Use of prenatal vitamins or multivitamins — no. (%)	3903 (76.7)	3889 (76.8)
Daily dose of vitamin C — mg		
Median	120	100
Interquartile range	50–120	50–120
Daily dose of vitamin E — IU		
Median	22	22
Interquartile range	3–30	0–30
Previous pregnancy — no. (%)	1161 (22.8)	1170 (23.1)
Family history of preeclampsia — no. (%)§	650 (12.8)	674 (13.3)
Blood pressure — mm Hg		
Systolic	109±10	109±10
Diastolic	66±8	65±8

* Plus–minus values are means ±SD. P≥0.05 for all between-group comparisons.
† Race or ethnic group was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Prepregnancy weight used to calculate body-mass index was self-reported. Values were unavailable for 99 women in the vitamin group and 111 in the placebo group.
§ Family history is based on self-reported preeclampsia in a first-degree relative (mother, sister, or grandmother).

RESULTS

STUDY POPULATION

Figure 1 shows the enrollment and follow-up of the women who participated in the trial. A total of 10,154 women were randomly assigned to a study group; 5088 were assigned to receive vitamins, and 5066 to receive placebo. Data for two women were removed, one at the patient's request and one at the request of the institutional review board at her site (after a lapse in approval by the institutional review board at that site), resulting in a total of 10,152 women. A total of 94 women in the vitamin group and 89 women in the placebo group (1.8% overall) were lost to follow-up.

Baseline characteristics were similar between the two groups (Table 1). A total of 77% of the enrolled subjects were taking a prenatal vitamin or multivitamin at the time of randomization. Among the 9969 women for whom pregnancy outcome data were available, the median ratio of the number of study capsules taken to the number that should have been taken, between the time of randomization and delivery, was 88% in both study groups. Side effects were reported by 11.2% of the women. There were no significant between-group differences in the rates of any of the reported side effects. The most common side effects were nausea (7.3% in the vitamin group and 6.8% in the placebo group, P=0.31) and vomiting (4.4% in the vitamin group and 4.0% in the placebo group, P=0.23).

STUDY OUTCOMES

The criteria for the primary outcome were met by 305 women in the vitamin group (6.1%), as compared with 285 in the placebo group (5.7%) (relative risk, 1.07; 95% confidence interval [CI], 0.91 to 1.25). There was no significant between-group difference in any component of the primary outcome (Table 2). Rates of maternal secondary outcomes are shown in Table 3. There was no significant difference in the rate of preeclampsia between the women in the vitamin group and those in the placebo group (7.2% and 6.7%, respectively). Among the women who met the criteria for the primary outcome, 164 (27.8%) had severe hypertension only and 321 (54.4%) had preeclampsia (of whom 40 had mild preeclampsia; 257, severe preeclampsia; 10, the HELLP syndrome; and 14, eclampsia). No benefit of therapy was seen in women with severe pregnancy-associated hypertension or mild preeclampsia with one of the primary outcome components (relative risk, 1.07; 95% CI, 0.89 to 1.27). Two women (one in each study group) died from peripartum cardiomyopathy. Rates of adverse neonatal outcomes also did not differ significantly between the groups (Table 4).

We performed one post hoc subgroup analysis on the basis of the week of pregnancy at randomization (<13 weeks vs. ≥13 weeks). Results did not differ significantly according to subgroup (P=0.54 for the interaction). Among the 4343 women who entered the study before the 13th

Table 2. Primary Outcome and Components.

Outcome	Vitamins (N=4993)	Placebo (N=4976)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary composite outcome*	305 (6.1)	285 (5.7)	1.07 (0.91–1.25)	0.42
Severe hypertension†	210 (4.2)	204 (4.1)	1.03 (0.85–1.24)	0.79
Mild or severe hypertension‡				
With elevated liver-enzyme levels	26 (0.5)	33 (0.7)	0.79 (0.47–1.31)	0.35
With thrombocytopenia	21 (0.4)	31 (0.6)	0.68 (0.39–1.17)	0.16
With creatinine level ≥1.5 mg/dl (133 μmol/liter)	7 (0.1)	11 (0.2)	0.63 (0.25–1.63)	0.34
With eclamptic seizure	10 (0.2)	4 (0.1)	2.49 (0.78–7.94)	0.11
With medically indicated preterm birth, at <32 weeks' gestation, due to hypertensive disorder	13 (0.3)	16 (0.3)	0.81 (0.39–1.68)	0.57
With small-for-gestational-age baby§	60 (1.2)	46 (0.9)	1.30 (0.89–1.90)	0.18
With fetal or neonatal death	12 (0.2)	11 (0.2)	1.09 (0.48–2.46)	0.84

* The primary composite outcome was severe pregnancy-associated hypertension alone or severe or mild hypertension with elevated liver-enzyme levels, thrombocytopenia, elevated serum creatinine levels, eclamptic seizure, indicated preterm birth, fetal-growth restriction, or perinatal death. Women were counted only once, regardless of the number of events.

† Included here are women who had severe hypertension only and those who had severe hypertension with elevated liver-enzyme levels, thrombocytopenia, elevated serum creatinine levels, eclamptic seizure, medically indicated preterm birth, fetal-growth restriction, or perinatal death.

‡ Women who met more than one component of the primary outcome were counted for each component. Therefore, the number of women for all individual components combined is greater than the number of women with the primary outcome.

§ A baby whose weight was less than the 3rd percentile was considered to be small for gestational age.

week of pregnancy, the primary outcome occurred in 6.6% of those in the vitamin group, as compared with 5.9% of those in the placebo group (relative risk, 1.12; 95% CI, 0.89 to 1.42); among the 5626 women who were enrolled in or after the 13th week of pregnancy, the primary outcome occurred in 5.7% of those in the vitamin group and 5.6% of those in the placebo group (relative risk, 1.02; 95% CI, 0.82 to 1.26).

DISCUSSION

In our study, supplementation with vitamins C and E did not reduce the frequency of the primary outcome or any of its components. We chose the primary outcome of new-onset pregnancy-associated hypertension with evidence of maternal, fetal, or neonatal complications, rather than the diagnosis of preeclampsia, so that we could assess whether therapy would prevent serious complications rather than merely modify diagnostic findings. We did not require the presence of proteinuria as part of the primary outcome, since severe hypertension without proteinuria can be associated with adverse maternal and fetal outcomes.[20] Furthermore, a diagnosis of proteinuria that is based on the qualitative assessment of random urine samples or even on protein-to-creatinine ratios cannot be compared with a diagnosis that is based on 24-hour urine collections.[21-24] Since our primary outcome was not based on a conventional diagnosis of preeclampsia, we used preeclampsia as a major secondary outcome. The rates of mild preeclampsia, severe preeclampsia, the HELLP syndrome, and eclampsia were not significantly affected by vitamin treatment. There was also no evidence of a benefit with vitamin therapy with respect to any of the other prespecified secondary outcomes.

Several other trials have examined the effectiveness of vitamins C and E in preventing preeclampsia.[11-14] The doses of vitamins that were used in those trials were the same as those used in our trial. Each of the previous trials had a smaller sample than that in our study; only one of the previous trials included low-risk subjects.[13] In no other study was therapy initiated as early as it was in our trial. The Vitamins in Pre-eclampsia

Table 3. Secondary Maternal Outcomes.*

Outcome	Vitamins (N=4993)	Placebo (N=4976)	Relative Risk (95% CI)	P Value
Preeclampsia — no. (%)	358 (7.2)	332 (6.7)	1.07 (0.93–1.24)	0.33
Mild	212 (4.2)	191 (3.8)		
Severe	134 (2.7)	129 (2.6)		
HELLP syndrome	2 (<0.1)	8 (0.2)		
Eclampsia	10 (0.2)	4 (0.1)		
Pregnancy-associated hypertension — no. (%)	1457 (29.2)	1322 (26.6)	1.10 (1.03–1.17)	0.004
Medically indicated delivery because of hypertension — no./total no. (%)	509/4952 (10.3)	473/4934 (9.6)	1.07 (0.95–1.21)	0.25
Aspartate aminotransferase ≥100 U/liter — no. (%)	35 (0.7)	48 (1.0)	0.73 (0.47–1.12)	0.15
Creatinine ≥1.5 mg/dl (133 μmol/liter) — no. (%)	9 (0.2)	12 (0.2)	0.75 (0.32–1.77)	0.51
Antepartum bleeding — no./total no. (%)	56/4956 (1.1)	46/4937 (0.9)	1.21 (0.82–1.79)	0.33
Premature rupture of membranes — no./total no. (%)	124/4934 (2.5)	129/4923 (2.6)	0.96 (0.75–1.22)	0.74
Placental abruption — no./total no. (%)	24/4957 (0.5)	36/4938 (0.7)	0.66 (0.40–1.11)	0.12
Cesarean delivery — no./total no. (%)	1269/4958 (25.6)	1224/4940 (24.8)	1.03 (0.97–1.11)	0.35
Maternal death — no. (%)	1 (<0.1)	1 (<0.1)	—	—
Postpartum pulmonary edema — no./total no. (%)	3/4951 (0.1)	10/4926 (0.2)	0.30 (0.08–1.08)	0.05
Hematocrit ≤24% with transfusion — no./total no. (%)	40/4954 (0.8)	59/4927 (1.2)	0.67 (0.45–1.01)	0.05
Hospital stay — days				0.65
Median	2.0	2.0		
Interquartile range	2.0–3.0	2.0–3.0		

* HELLP denotes hemolytic anemia, elevated liver enzymes, and low platelet count.

study (VIP; Current Controlled Trials number, ISRCTN62368611) of antioxidant supplementation to prevent preeclampsia in high-risk women showed that there was an increased rate of complications among women and infants when women received antioxidant vitamins during pregnancy.[14] In that study, there were significantly more babies with low birth weight (a prespecified outcome) in the group that received vitamin supplementation than in the control group; gestational hypertension and the use of antihypertensive therapy were also more common in the vitamin group. Although the rates of perinatal death were similar in the two groups, post hoc analyses showed that the stillbirth rate was higher (and the neonatal death rate lower) in the vitamin group than in the control group. In contrast, we did not find significant between-group differences in the rates of low birth weight and stillbirth. We did find an increase in the frequency of gestational hypertension in the vitamin group, as compared with the placebo group. We did not collect data on the use of antihypertensive medications, but a significant increase in the use of antihypertensive therapy was found with vitamin supplementation in the previous trial involving low-risk women.[13]

Why was therapy with these antioxidant vitamins not successful in altering the outcome of hypertension in pregnancy in our study or in previous studies? It is, of course, possible that although oxidative stress is present in preeclampsia, it is not important in the pathophysiology of the condition. Alternatively, oxidative stress may be relevant to pathogenesis in only a subgroup of women, with no appreciable benefit of antioxidants for the overall population. It has been suggested, in relation to other trials, that the women may already have had adequate concentrations of vitamins C and E before therapy.[25] In our study, almost 80% of the women were taking prenatal vitamins that contained an average of 100 mg of vitamin C and 22 IU of alpha-tocopherol when they entered the study. Doses of ascorbate of 150 mg per day result in nearly maximal plasma and tissue concentrations. Administration of 1000 mg per day increases the plasma concentration by

Table 4. Secondary Neonatal Outcomes.*

Outcome	Vitamins (N=4993)	Placebo (N=4976)	Relative Risk (95% CI)	P Value
Gestational age at delivery — wk	38.9±3.5	38.8±3.5		0.21
Preterm birth — no. (%)				
<37 weeks' gestation	513 (10.3)	526 (10.6)	0.97 (0.87–1.09)	0.63
<32 weeks' gestation	149 (3.0)	173 (3.5)	0.86 (0.69–1.06)	0.16
Fetal or neonatal death — no. (%)	113 (2.3)	122 (2.5)	0.92 (0.72–1.19)	0.53
Fetal loss at <20 weeks	55 (1.1)	59 (1.2)		
Fetal death at ≥20 weeks	38 (0.8)	36 (0.7)		
Neonatal death	20 (0.4)	27 (0.5)		
Liveborn infants — no.	4900	4881		
Birth weight — g	3247±575	3244±581		0.55
Small for gestational age — no. of liveborn infants (%)†	133 (2.7)	132 (2.7)	1.00 (0.79–1.27)	0.98
Birth weight <2500 g — no. of liveborn infants (%)	345 (7.0)	369 (7.6)	0.93 (0.81–1.07)	0.32
Admission to NICU — no. of liveborn infants (%)	577 (11.8)	557 (11.4)	1.03 (0.92–1.15)	0.58
Respiratory distress syndrome — no. of liveborn infants (%)	150 (3.1)	144 (3.0)	1.04 (0.83–1.30)	0.75
Intraventricular hemorrhage, grade III or IV — no. of liveborn infants (%)	6 (0.1)	7 (0.1)	0.85 (0.29–2.54)	0.78
Sepsis — no. of liveborn infants (%)	30 (0.6)	23 (0.5)	1.30 (0.76–2.23)	0.34
Necrotizing enterocolitis — no. of liveborn infants (%)	10 (0.2)	14 (0.3)	0.71 (0.32–1.60)	0.41
Retinopathy of prematurity — no. of liveborn infants (%)	19 (0.4)	16 (0.3)	1.18 (0.61–2.30)	0.62
Apgar score ≤3 at 5 min — no. of liveborn infants (%)	23 (0.5)	27 (0.6)	0.85 (0.49–1.48)	0.56
Hospital stay — days				0.79
Median	2.0	2.0		
Interquartile range	2.0–3.0	2.0–3.0		

* Plus–minus values are means ±SD. NICU denotes neonatal intensive care unit.
† A baby whose birth weight was less than the 3rd percentile was considered to be small for gestational age.

only 25% above that achieved with 150 mg per day.[26] The doses of alpha-tocopherol used in this study, however, would be expected to increase plasma concentrations substantially above those achieved with prenatal vitamins.[26] The possibility that therapy might be effective specifically in women who are deficient in these vitamins was not supported by the World Health Organization study (ISRCTN86677348) of vitamin C and E supplementation, which showed that supplementation with these vitamins, as compared with placebo, did not reduce the risk of preeclampsia in a high-risk and nutritionally deficient population (relative risk with vitamins, 1.0; 95% CI, 0.9 to 1.3).[11]

The doses of vitamins C and E used in our trial were determined on the basis of the preliminary study, in which these doses not only appeared to reduce the frequency of preeclampsia but also decreased objective evidence of oxidative stress.[10] The timing of the administration of antioxidants is also important. The antioxidants need to be present at the time of a relevant pro-oxidant challenge. Burton and Jauniaux found that the initiation of intervillous blood flow at 8 to 10 weeks of gestation was associated with a burst of oxidative stress.[27] Antioxidant therapy in our study was initiated in the 9th to 16th week of pregnancy, with 44% of women beginning treatment before the 13th week of pregnancy. In a post hoc subgroup analysis limited to women treated before the 13th week of pregnancy, there was no apparent benefit of vitamin supplementation. We also cannot be certain that other antioxidants would not have been effective.

In summary, supplementation with vitamin C (at a dose of 1000 mg daily) and vitamin E (at a dose of 400 IU daily) did not reduce the rates of

either serious adverse outcomes of pregnancy-associated hypertension or preeclampsia among low-risk, nulliparous women. Previous studies have shown a similar lack of efficacy among high-risk women and among women who were likely to have had a deficiency of vitamins C and E. The findings of these several studies provide no support for the use of vitamin C and E supplementation in pregnancy to reduce the risk of preeclampsia or its complications.

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