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ORIGINAL ARTICLE

Vitamins C and E and the Risks of Preeclampsia and Perinatal Complications

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ABSTRACT

BACKGROUND

Supplementation with antioxidant vitamins has been proposed to reduce the risk of preeclampsia and perinatal complications, but the effects of this intervention are uncertain.

METHODS

We conducted a multicenter, randomized trial of nulliparous women between 14 and 22 weeks of gestation. Women were assigned to daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E or placebo (microcrystalline cellulose) until delivery. Primary outcomes were the risks of maternal preeclampsia, death or serious outcomes in the infants (on the basis of definitions used by the Australian and New Zealand Neonatal Network), and delivering an infant whose birth weight was below the 10th percentile for gestational age.

RESULTS

Of the 1877 women enrolled in the study, 935 were randomly assigned to the vitamin group and 942 to the placebo group. Baseline characteristics of the two groups were similar. There were no significant differences between the vitamin and placebo groups in the risk of preeclampsia (6.0 percent and 5.0 percent, respectively; relative risk, 1.20; 95 percent confidence interval, 0.82 to 1.75), death or serious outcomes in the infant (9.5 percent and 12.1 percent; relative risk, 0.79; 95 percent confidence interval, 0.61 to 1.02), or having an infant with a birth weight below the 10th percentile for gestational age (8.7 percent and 9.9 percent; relative risk, 0.87; 95 percent confidence interval, 0.66 to 1.16).

CONCLUSIONS

Supplementation with vitamins C and E during pregnancy does not reduce the risk of preeclampsia in nulliparous women, the risk of intrauterine growth restriction, or the risk of death or other serious outcomes in their infants. (Controlledtrials.com number, ISRCTN00416244.)

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Preeclampsia is a multisystem disorder characterized by hypertension and proteinuria occurring in the second half of pregnancy.[1] Nulliparity is a recognized risk factor. Preeclampsia carries risks of serious complications and death for the mother.[1-3] For the infant, risks include death, preterm birth, intrauterine hypoxia, and poor intrauterine growth.[1,4,5]

The pathogenesis of preeclampsia involves inadequate trophoblast invasion,[6] often leading to poor placental perfusion; generalized endothelial dysfunction[7]; and immune maladaptation and inflammation.[8] Oxidative stress, characterized by excessive production of reactive oxygen species, coupled with inadequate or overwhelmed antioxidant defense mechanisms, has been proposed as a link between these events.

Antioxidants are important in maintaining cellular integrity in a normal pregnancy by inhibiting peroxidation reactions and thus protecting enzymes, proteins, and cells from destruction by peroxides. Antioxidant defense mechanisms include cellular and extracellular enzymes such as glutathione reductase, superoxide dismutase, catalase, and free-radical scavengers, including vitamins C and E, carotenoids, glutathione, serum albumin, and metabolites such as bilirubin and uric acid. Vitamins C and E are antioxidants derived from the diet. Vitamin C scavenges free radicals in the aqueous phase, and the lipid-soluble vitamin E acts in vivo to prevent the formation of lipid peroxides and thus protect cell membranes.

There is evidence of oxidative stress in women with established preeclampsia, including increased plasma concentrations of 8-epi-prostaglandin $F_{2\alpha}$,[9] lipid peroxides,[10] and decreased concentrations of antioxidants such as vitamins C and E.[11] Oxidative stress is implicated in complications affecting preterm infants, including the respiratory distress syndrome, chronic lung disease, intraventricular hemorrhage, retinopathy of prematurity, and necrotizing enterocolitis.[12,13] These observations led to the premise that prophylaxis with antioxidants may prevent oxidative stress and thereby reduce the risk of both preeclampsia in pregnant women and perinatal complications in their infants.

An initial randomized trial of prophylactic supplementation with antioxidants provided during pregnancy to 283 women at risk for preeclampsia, as compared with women not receiving antioxidant supplementation, showed a significant reduction in preeclampsia (8 percent vs. 17 percent) and a nonsignificant reduction in the risk of the infant's being small for gestational age.[14] However, a subsequent trial of antioxidants in 109 women reported no significant reduction in the risk of preeclampsia (17 percent, vs. 19 percent in the placebo group).[15] There is limited information about the effects of antioxidants on serious health outcomes in infants and on whether there may be benefits independent of a reduction in preeclampsia. There have been calls for further randomized trials in populations that have a different risk of preeclampsia to assess the efficacy and safety of antioxidant supplementation.[1,14,15]

We designed the Australian Collaborative Trial of Supplements (ACTS) with vitamin C and vitamin E to assess whether supplementation reduced perinatal complications in nulliparous women and their infants, including preeclampsia, death, or serious outcomes, and small size for gestational age.

METHODS

STUDY DESIGN AND POPULATION

We conducted a multicenter, randomized trial involving nulliparous women with a singleton pregnancy between 14 and 22 weeks of gestation. Eligible women had normal blood pressure at the first measurement in pregnancy and again at trial entry. Women with any of the following were ineligible: known multiple pregnancy, known potentially lethal fetal anomaly, known thrombophilia, chronic renal failure, antihypertensive therapy, or specific contraindications to vitamin C or E therapy such as hemochromatosis or anticoagulant therapy.[16]

The protocol was approved by the research and ethics committees at the nine collaborating hospitals. All women provided written informed consent.

INTERVENTION

The treatment packs contained four sealed, opaque, white plastic bottles of either the antioxidants vitamin C and vitamin E or the placebo and were prepared by a researcher not involved in recruitment or clinical care. Stratification was according to collaborating center and gestational age (less than 18 weeks vs. 18 weeks or more).

Randomization was performed through a central telephone randomization service. Women assigned to the vitamin group were advised to take four coated tablets of a combination of 250 mg of vitamin C (as ascorbic acid) and 100 IU of vitamin E (as *d*-alpha-tocopherol succinate) each day from trial entry until they gave birth. The total daily dose of vitamin C was 1000 mg, and that of vitamin E, 400 IU. Women assigned to placebo were advised to take four tablets daily containing microcrystalline cellulose, which were similarly coated and identical in appearance to the vitamin tablets.

Women were asked to swallow the tablets whole without crushing or chewing them and were advised to take two tablets in the morning and two tablets in the evening. They were advised not to take any other antioxidant supplements, although a multivitamin preparation that provided a daily intake of no more than 200 mg of vitamin C or 50 IU of vitamin E was permitted. All infants in the study were recommended to receive intramuscular vitamin K after birth.[16]

The care that the women and their infants received was according to standard practice at each center, with surveillance for hypertension with the use of standardized measurements of blood pressure.[17] Korotkoff phase V was used to measure diastolic blood pressure unless the diastolic blood pressure was 0 mm Hg, in which case Korotkoff phase IV was used. If the woman's blood pressure was elevated, urinalysis for proteinuria was recommended.

The women completed a food-frequency questionnaire at trial entry to assess dietary intake.[18] Adherence to and the side effects of treatment were assessed by self-completed questionnaires that the women answered postnatally. Women were specifically asked how often they missed taking the trial tablets and how many times a week they missed taking all the tablets. Adherence was defined by consumption of at least 80 percent of all tablets at recommended times.

OUTCOME VARIABLES

There were three primary outcomes: the development of preeclampsia in the mother, a composite measure of death or serious outcomes in the infant, and the birth of an infant who was small for gestational age. Preeclampsia was defined as hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure [Korotkoff V] ≥90 mm Hg on at least two occasions four or more hours apart, or both) arising after 20 weeks' gestation and one or more of the following: proteinuria, renal insufficiency, liver disease, neurologic problems, hematologic disturbances, or fetal-growth restriction[17] (Table 1). The composite measure of serious outcomes in the infant was defined as one or more of the following: fetal death after trial entry (categorized as either before 20 weeks' gestation, or at 20 weeks' gestation or later); death of a live-born infant before hospital discharge; birth weight below the 3rd percentile for gestational age; severe respiratory distress syndrome (defined by a mean airway pressure of ≥10 mm Hg or a fraction of inspired oxygen of ≥0.80 cm of water, or both); chronic lung disease; intraventricular hemorrhage of grade 3 or 4; cystic periventricular leukomalacia; retinopathy of prematurity of stage 3 or 4; necrotizing enterocolitis; Apgar score of less than 4 at 5 minutes; seizures before 24 hours of age or requiring two or more drugs to control; hypotonia for at least 2 hours; stupor; decreased response to pain; coma; tube feeding for 4 or more days; care in the neonatal intensive care unit for more than 4 days; or use of ventilation for 24 hours or more. These definitions of serious outcomes are based on those used by the Australian and New Zealand Neonatal Network[19] and are important measures of morbidity at or beyond term.[20] Small size for gestational age was defined by a birth weight below the 10th percentile for gestation according to fetal sex on standardized birth-weight charts.[21]

Secondary outcomes in the infants included serious complications occurring before hospital discharge. For the women, secondary outcomes included a composite of any of the following until six weeks post partum: death, pulmonary edema, eclampsia, stroke, thrombocytopenia, renal insufficiency, respiratory distress syndrome, cardiac arrest, respiratory arrest, placental abruption, abnormal liver function, preterm prelabor rupture of membranes, major postpartum hemorrhage, postpartum pyrexia, pneumonia, deep-vein thrombosis, or pulmonary embolus requiring anticoagulant therapy. Other outcomes included antenatal, intrapartum, and postnatal end points, particularly those related to hypertensive disease, including the need for antenatal hospitalization or antenatal care during the day for hypertension, need for induction of labor for hypertension, use of antihypertensive agents, and use of magnesium sulfate.

Table 1. Primary Study Outcomes.

Outcome	Vitamin Group (N=935)	Placebo Group (N=942)	Relative Risk (95% CI)*	P Value†
	number (percent)			
Women				
Preeclampsia‡	56 (6.0)	47 (5.0)	1.20 (0.82–1.75)	0.57
Infants				
Death or serious outcome	89 (9.5)	114 (12.1)	0.79 (0.61–1.02)	0.20
Small for gestational age§	80 (8.7)	92 (9.9)	0.87 (0.66–1.16)	0.57

* CI denotes confidence interval (unadjusted).
† P values were adjusted for multiple comparisons.
‡ Preeclampsia was defined as hypertension occurring with one or more of the following: proteinuria, defined as ≥300 mg of protein per 24 hours or a ratio of protein to creatinine of ≥30 mg per millimole in a "spot" urine specimen; renal insufficiency, defined by a serum or plasma creatinine level ≥0.09 mmol per liter (≥1.02 mg per deciliter) or oliguria (<30 ml of urine per hour for ≥6 hours); liver disease, defined by an aspartate aminotransferase or alanine aminotransferase level of >50 IU per liter, severe epigastric or right-upper-quadrant pain, or both; neurologic problems, defined as convulsions (eclampsia); hyperreflexia with clonus; severe headaches with hyperreflexia or persistent visual disturbances (scotomata); hematologic disturbances (thrombocytopenia, defined by a platelet count of <100,000 per cubic millimeter; disseminated intravascular coagulation, defined by an international normalized ratio of >1.5, an activated partial-thromboplastin time >5 seconds longer than the laboratory reference value, or a fibrinogen level of <1 g per liter; hemolysis, defined by a lactate dehydrogenase level >500 IU per liter, fragmentocytes on peripheral-blood smear, or both); or fetal growth restriction, defined by a birth weight below the 10th percentile for gestational age. The number of women with hypertension and one or more of the following abnormalities were as follows: proteinuria, 4.7 percent in the vitamin group and 2.8 percent in the placebo group; renal insufficiency, 1.0 percent and 0.3 percent, respectively; liver disease, 2.4 percent and 0.6 percent; neurologic problems, 1.8 percent and 1.8 percent; hematologic disturbances, 0.6 percent and 0.1 percent; and fetal growth restriction, 0.9 percent and 1.2 percent.
§ The analysis included 924 live-born infants in the vitamin group and 929 live-born infants in the placebo group.

STATISTICAL ANALYSIS

Analyses were performed on an intention-to-treat basis with the use of SAS software, version 9.1. No adjustments were made, since prognostic factors were balanced at trial entry between the two groups. Relative risks with 95 percent confidence intervals are used for dichotomous variables. Continuous variables, if normally distributed, were analyzed with the use of Student's t-test, and nonparametric tests were used for skewed data. For the small number of twins (four pairs) in the study, outcomes for one randomly selected infant in each pair of twins were included in the analyses. A P value of less than 0.05 was considered to indicate statistical significance. All P values were two-sided. A step-down Sidak adjustment was made for the analyses involving multiple primary end points, with adjusted P values reported.[22]

We estimated that a sample size of 1870 women would have a statistical power of 80 percent (two-tailed alpha level of 0.05) to detect a reduction in the risk of death or serious outcomes in the infants from 6.5 percent to 3.7 percent[23] (and Clinical Information Services at the Women's and Children's Hospital, Adelaide). Although our trial was powered to focus on the serious outcomes for the infant, we estimated that this sample size would also have a statistical power of 80 percent to detect a reduction in the risk of preeclampsia among the women from 10.0 percent to 6.3 percent. An interim analysis was not performed. The treatment allocation was broken after the analyses were completed. The suppliers of the tablets were not involved in any other aspect of the study including design, data management, or preparation of the manuscript.

RESULTS

Of the 1877 women enrolled, 935 (49.8 percent) were assigned to the vitamin group and 942 (50.2 percent) to the placebo group (Fig. 1). Recruitment started in December 2001 and was completed in January 2005. Clinical outcomes were available up until hospital discharge for all the women who underwent randomization and their infants.

At study entry, maternal baseline characteristics in the two groups were similar, including median dietary intake of vitamins C and E (Ta-

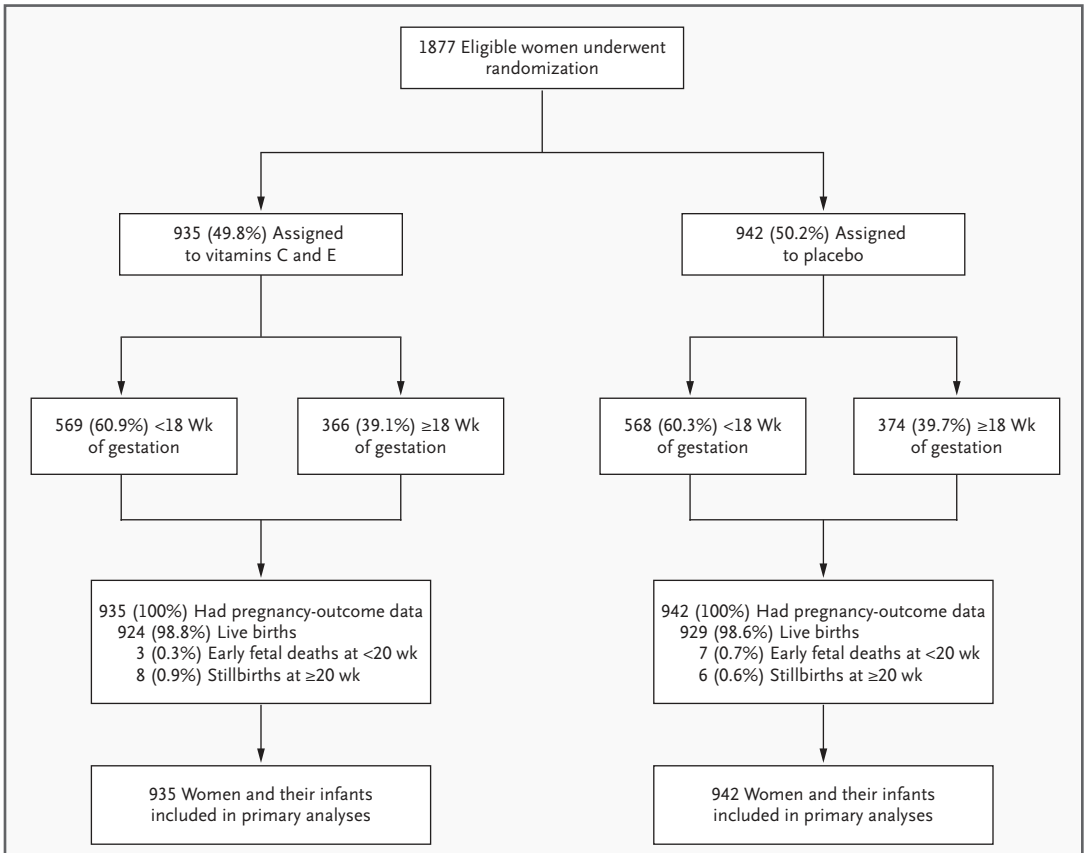

Figure 1. Disposition of Women and Their Infants in the Trial.
Live births included one neonate in the vitamin group (0.1 percent) and four in the placebo group (0.4 percent) who died before hospital discharge.

ble 2). There was no significant difference in estimated adherence between the vitamin group and the placebo group (66.6 percent vs. 69.9 percent; relative risk, 0.95; 95 percent confidence interval, 0.89 to 1.02).

PRIMARY OUTCOMES

There were no significant differences between the vitamin group and the placebo group in the risk of preeclampsia (6.0 percent and 5.0 percent, respectively; relative risk, 1.20; 95 percent confidence interval, 0.82 to 1.75), the risk of death or serious outcomes in the infants (9.5 percent and 12.1 percent; relative risk, 0.79; 95 percent confidence interval, 0.61 to 1.02), or the risk of having an infant who was small for gestational age (8.7 percent and 9.9 percent; relative risk, 0.87; 95 percent confidence interval, 0.66 to 1.16) (Table 1).

SECONDARY OUTCOMES

When the individual outcomes included in the composite end point of death or serious outcomes in the infants were examined, there were no significant differences for any of the outcomes between the two groups (Table 3). The rate of preterm birth was similar in the two groups (Table 4). As compared with infants in the placebo group, significantly fewer of those in the vitamin group had the respiratory distress syndrome (0.2 percent vs. 1.3 percent; relative risk, 0.17; 95 percent confidence interval, 0.04 to 0.75) and fewer required surfactant (0.2 percent vs. 1.0 percent; relative risk, 0.22; 95 percent confidence interval, 0.05 to 1.03) (Table 4). There was no significant difference between the two groups of infants in the need for mechanical ventilation or the risk of other adverse outcomes, including measures of growth (Table 4).

Table 2. Baseline Maternal Characteristics.*

Characteristic	Vitamin Group (N=935)	Placebo Group (N=942)
Age — yr	26.3±5.6	26.6±5.8
Gestational age — wk	17.1±2.3	17.1±2.3
Blood pressure — mm Hg		
Systolic	110.3±10.9	110.1±10.4
Diastolic	65.5±8.1	65.5±8.1
Body-mass index†		
Median	24.0	24.2
Interquartile range	21.3–27.7	21.7–27.5
Previous pregnancies lasting <20 wk — no. (%)	269 (28.8)	278 (29.5)
Race or ethnic group — no. (%)‡		
White	891 (95.3)	886 (94.1)
Asian	27 (2.9)	32 (3.4)
Other	17 (1.8)	24 (2.5)
Smoker — no. (%)†	210 (22.5)	195 (20.7)
Level of education — no. (%)		
Secondary or lower	435 (46.5)	424 (45.0)
Postsecondary training program	215 (23.0)	229 (24.3)
University studies	285 (30.5)	289 (30.7)
Adequate dietary intake of vitamin C§		
Intake of vitamin C — no./total no. (%)	777/831 (93.5)	772/834 (92.6)
Median — mg	201.8	208.9
Interquartile range — mg	137.1–309.2	134.9–317.0
Adequate dietary intake of vitamin E§		
Intake of vitamin E — no./total no. (%)	359/831 (43.2)	354/834 (42.4)
Median — mg	8.7	8.8
Interquartile range — mg	5.9–14.5	5.7–15.1
Family history of preeclampsia — no./total no. (%)¶	173/914 (18.9)	166/924 (18.0)

* Plus–minus values are means ±SD. Body-mass index is the weight in kilograms divided by the square of the height in meters.
† Data are from information obtained at the first antenatal visit in the first trimester.
‡ Race or ethnic group was self-reported.
§ Adequate dietary intake was defined as an intake at or above the recommended daily allowances in pregnancy (vitamin C, ≥70 mg and vitamin E, ≥10 mg α-tocopherol equivalent)[24] on the basis of dietary information.
¶ Family history is based on self-reports of preeclampsia in an immediate female relative such as mother, sister, or grandmother.

The risk of death or serious outcomes did not differ significantly between the women in the vitamin group and those in the placebo group (10.1 percent vs. 7.7 percent; relative risk, 1.30; 95 percent confidence interval, 0.97 to 1.74) (Table 5). No significant differences were seen between the groups for any of the individual components of the composite maternal end point apart from a higher frequency of abnormal results on liver-function tests (raised aminotransferase levels) in the vitamin group; testing was performed only in the subgroup of women considered to have clinical indications for testing.

Women in the vitamin group had an increased risk of being admitted antenatally for hypertension and being prescribed antihypertensive drugs (Table 4). There were no significant differences between the two groups in the timing of detec-

Table 3. Serious Outcomes in the Infants.*

Outcome	Vitamin Group (N=935)	Placebo Group (N=942)	Relative Risk (95% CI)
	number (percent)		
Fetal loss or death of infant	12 (1.3)	17 (1.8)	0.71 (0.34–1.48)
Early fetal death	3 (0.3)	7 (0.7)	0.43 (0.11–1.66)
Stillbirth	8 (0.9)	6 (0.6)	1.34 (0.47–3.86)
Neonatal death	1 (0.1)	4 (0.4)	0.25 (0.03–2.24)
Live birth	924 (98.8)	929 (98.6)	
≥4 Days of tube feeding†	40 (4.3)	54 (5.8)	0.74 (0.50–1.11)
Severe IUGR (≥3rd percentile)†	23 (2.5)	36 (3.9)	0.64 (0.38–1.08)
≥2 Hr of hypotonia†	14 (1.5)	14 (1.5)	1.01 (0.48–2.10)
>4 Days of NICU care†	9 (1.0)	15 (1.6)	0.60 (0.27–1.37)
≥24 Hr of ventilation†	9 (1.0)	14 (1.5)	0.65 (0.28–1.49)
Stupor, decreased response to pain, or coma†	9 (1.0)	5 (0.5)	1.81 (0.61–5.38)
Seizure <24 hr of age or controlled by ≥2 drugs†	4 (0.4)	1 (0.1)	4.02 (0.45–35.9)
Apgar score <4 at 5 min†	3 (0.3)	3 (0.3)	1.01 (0.20–4.97)
Severe RDS†‡	1 (0.1)	3 (0.3)	0.34 (0.03–3.22)
Chronic lung disease†§	1 (0.1)	5 (0.5)	0.20 (0.02–1.72)
Grade 3 or 4 intraventricular hemorrhage†	1 (0.1)	1 (0.1)	1.01 (0.06–16.0)
Cystic periventricular leukomalacia†	0	1 (0.1)	—
ROP requiring treatment†	0	1 (0.1)	—
Necrotizing enterocolitis†	0	2 (0.2)	—

* CI denotes confidence interval (unadjusted), IUGR intrauterine growth restriction, NICU neonatal intensive care unit, RDS respiratory distress syndrome, and ROP retinopathy of prematurity.
† The analysis included 924 live-born infants in the vitamin group and 929 live-born infants in the placebo group.
‡ Severe RDS was defined by a mean airway pressure of ≥10 mm Hg, a fraction of inspired oxygen of ≥0.80 cm of water, or both.
§ Chronic lung disease was defined as the need for oxygen at 36 weeks of postconceptual age for infants born at less than 32 weeks' gestation or the need for oxygen on day 28 for infants born at 32 weeks' gestation or more.

tion of preeclampsia, severity of disease, use of magnesium sulfate, or induction of labor because of hypertension (Table 4). There were also no significant differences in other antenatal, intrapartum or postnatal outcomes in self-reported side effects apart from a higher incidence of abdominal pain during late pregnancy in the vitamin group than the placebo group (7.9 percent vs. 4.8 percent; relative risk, 1.63; 95 percent confidence interval, 1.12 to 2.36).

DISCUSSION

In this randomized, placebo-controlled trial, giving healthy nulliparous women supplements of 1000 mg of vitamin C and 400 IU of vitamin E daily during pregnancy did not reduce their risk of preeclampsia, the risk of death or serious outcomes in their infants, or the risk of intrauterine growth restriction. This finding contrasts with the findings in an earlier trial that supplementation with vitamins C and E was beneficial in women at high risk for preeclampsia.[14] In our study, women in the vitamin group were more likely than those in the placebo group to be admitted antenatally with hypertension and to be treated with antihypertensive drugs. The cause of these unexpected adverse findings is unknown. They may be chance findings; however, such research has suggested that antioxidants may promote DNA oxidation through an interaction between vitamin C and metal ions.[25]

For infants in our study, maternal vitamin supplementation was not associated with a reduc-

Table 4. Secondary Maternal and Infant Outcomes.*

Outcome	Vitamin Group	Placebo Group	Relative Risk (95% CI)
Women			
Total no.	935	942	
Detection of preeclampsia			
Median — wk	37.2	37.3	
Interquartile range — wk	35.5–38.6	35.2–39.0	
<34 wk — no. (%)	7 (0.7)	6 (0.6)	1.18 (0.40 to 3.48)
≥34 wk — no. (%)	49 (5.2)	41 (4.4)	1.20 (0.80 to 1.80)
Gestational hypertension — no. (%)	124 (13.3)	109 (11.6)	1.15 (0.90 to 1.46)
Severe gestational hypertension — no. (%)	29 (3.1)	21 (2.2)	1.39 (0.80 to 2.42)
Antenatal hospitalization for hypertension — no. (%)	49 (5.2)	32 (3.4)	1.54 (1.00 to 2.39)
Use of antihypertensive agents — no. (%)	43 (4.6)	26 (2.8)	1.67 (1.03 to 2.69)
Use of magnesium sulfate — no. (%)	12 (1.3)	7 (0.7)	1.73 (0.68 to 4.37)
Gestational diabetes — no. (%)†	35 (3.7)	33 (3.5)	1.07 (0.67 to 1.70)
Development of chorioamnionitis — no. (%)‡	6 (0.6)	11 (1.2)	0.55 (0.20 to 1.48)
Induction of labor — no. (%)§	311 (33.3)	283 (30.0)	1.11 (0.97 to 1.26)
For hypertension	70 (7.5)	51 (5.4)	1.38 (0.98 to 1.96)
Cesarean section — no. (%)	250 (26.7)	248 (26.3)	1.02 (0.87 to 1.18)
Elective	59 (6.3)	55 (5.8)	1.08 (0.76 to 1.54)
Emergency	191 (20.4)	193 (20.5)	1.00 (0.83 to 1.19)
Length of gestation — wk			
Median	40.0	40.1	
Interquartile range	39.0–41.0	39.0–41.0	
Infants			
Total no.¶	932	935	
Preterm birth — no. (%)			
<37 wk	64 (6.9)	63 (6.7)	1.02 (0.73 to 1.43)
<34 wk	20 (2.1)	19 (2.0)	1.06 (0.57 to 1.97)
<28 wk	6 (0.6)	6 (0.6)	1.00 (0.32 to 3.10)
Birth weight — g	3392±599	3386±584	6.0 (–48 to 59)
Length at birth — cm	50.4±3.2	50.3±3.2	0.0 (–0.3 to 0.3)
Head circumference — cm	34.5±1.9	34.4±2.0	0.1 (–0.1 to 0.3)
Respiratory distress syndrome — no. (%)‖	2 (0.2)	12 (1.3)	0.17 (0.04 to 0.75)
Use of surfactant — no. (%)‖	2 (0.2)	9 (1.0)	0.22 (0.05 to 1.03)
Use of mechanical ventilation — no. (%)‖	13 (1.4)	23 (2.5)	0.57 (0.29 to 1.11)

* Plus–minus values are means ±SD. CI denotes confidence interval (unadjusted).
† Gestational diabetes was defined as a result of at least 7.8 mmol per liter on a two-hour oral glucose-tolerance test.
‡ The analysis included women requiring antibiotic treatment.
§ Indications for the induction of labor in the vitamin group and the placebo group, respectively, are past due dates, 14.5 percent and 12.8 percent; hypertension, 7.5 percent and 5.4 percent; rupture of membranes, 5.6 percent and 4.9 percent; severe intrauterine growth restriction, 1.1 and 1.6 percent; and other indications, 5.2 percent and 5.8 percent.
¶ The number of infants includes live births and stillbirths but not fetal losses before 20 weeks' gestation.
‖ The analysis included 924 live-born infants in the vitamin group and 929 live-born infants in the placebo group.

Table 5. Secondary Maternal Outcomes.*

Outcome	Vitamin Group (N=935)	Placebo Group (N=942)	Relative Risk (95% CI)
	number (percent)		
Death or serious maternal outcome	94 (10.1)	73 (7.7)	1.30 (0.97–1.74)
Preterm PROM	30 (3.2)	23 (2.4)	1.31 (0.77–2.25)
Major postpartum hemorrhage†	27 (2.9)	28 (3.0)	0.97 (0.58–1.64)
Abnormal liver function‡	21 (2.2)	10 (1.1)	2.12 (1.00–4.47)
Postpartum pyrexia§	11 (1.2)	7 (0.7)	1.58 (0.62–4.07)
Renal insufficiency¶	9 (1.0)	5 (0.5)	1.81 (0.61–5.39)
Pneumonia	3 (0.3)	2 (0.2)	1.51 (0.25–9.02)
Coagulopathy	3 (0.3)	3 (0.3)	1.01 (0.20–4.98)
Thrombocytopenia	3 (0.3)	1 (0.1)	3.02 (0.31–29.0)
Placental abruption‖	3 (0.3)	1 (0.1)	3.02 (0.31–29.0)
Oliguria**	2 (0.2)	1 (0.1)	2.01 (0.18–22.2)
Pulmonary edema	1 (0.1)	1 (0.1)	1.01 (0.06–16.1)
Deep-vein thrombosis	0	1 (0.1)	—
Pulmonary embolus	0	1 (0.1)	—

* There were no cases of eclampsia, stroke, death, respiratory distress syndrome, cardiac arrest, or respiratory arrest in either study group. CI denotes confidence interval (unadjusted), and PROM prelabor rupture of membranes.
† Major postpartum hemorrhage was defined by a blood loss of ≥1500 ml or use of blood transfusion.
‡ Abnormal liver function was defined by levels of aspartate aminotransferase or alanine aminotransferase ≥50 IU per liter. Data are available only for a subgroup of women for whom testing was considered clinically indicated and whose test results were abnormal.
§ Postpartum pyrexia was defined as a temperature of ≥38.5°C on two occasions >24 hours apart.
¶ Renal insufficiency was defined by a serum creatinine level ≥0.09 mmol per liter.
‖ Placental abruption was defined as abdominal pain and bleeding before birth associated with a retroplacental clot at delivery.
** Oliguria was defined by the output of <30 ml of urine per hour for ≥6 hours.

tion in the risk of a composite end point including serious health outcomes or in the risk of intrauterine growth restriction. Although maternal supplementation was not associated with any overall benefits with respect to the primary infant outcomes, it was associated with a reduced risk of the respiratory distress syndrome and the use of surfactant. There was no significant difference in the rate of preterm birth between the two study groups. Oxidative stress has been implicated in diseases common among preterm infants, including the respiratory distress syndrome and chronic lung disease.[12,13] Maternal supplementation with antioxidant vitamins may increase the antioxidant status of at-risk infants and thus reduce the risk of diseases associated with oxidative stress, independent of any effects on preeclampsia and iatrogenic preterm birth. However, it remains possible that the isolated reductions in infant outcomes are due to chance, given that statistical adjustment was not made for multiple comparisons in the analyses of secondary outcomes.

Adherence to the trial medications in our study was similar to that in other supplementation trials involving nulliparous women.[23,26] We found no significant differences in adherence between the two groups. The doses we used are similar to those of two previous trials of supplementation with vitamins C and E.[14,15] Doses of vitamin C of 1000 mg per day,[27] which is the dose we used, result in plasma saturation. For vitamin E, doses of 400 IU per day have been shown to prevent low-density lipoprotein oxidation,[28] with limited evidence that higher doses (above 400 IU per day) are more effective. It is therefore unlikely that higher doses of these vitamins would have reduced the rate of preeclampsia.

The group receiving vitamin supplementation had a higher rate of elevated aminotransferase levels than did the placebo group. No increased

risk of abnormal liver function has been reported in previous randomized trials of supplementation with vitamins C and E in pregnancy[29] or in trials of high-dose supplementation outside pregnancy.[30] In our study, liver function was assessed only in women considered to have clinical indications for testing, and therefore, the results of testing are known only for a subgroup of women. This assessment was one of multiple comparisons performed, and the results may be due to chance; other studies of supplementation with vitamins C and E in pregnancy should assess liver-function tests.

The majority of the women we studied had a baseline dietary intake of vitamins C and E above the recommended daily amount.[24] Thus, the results cannot be generalized to women with low dietary intakes of antioxidants. An ongoing trial is assessing whether antioxidants are beneficial in such women.[31] Ongoing trials are also assessing whether antioxidant supplementation is beneficial for nulliparous women[32,33] and for women considered to be at increased risk for preeclampsia, including women with diabetes[34] and those who had preeclampsia during a previous pregnancy.[31,33,35]

Our results indicate that daily supplementation with 1000 mg of vitamin C and 400 IU of vitamin E does not reduce the risk of preeclampsia in nulliparous pregnant women or the risk of serious perinatal complications or poor intrauterine growth in their infants. Our results do not support routine supplementation with vitamins C and E during pregnancy to prevent preeclampsia or other adverse perinatal outcomes in nulliparous women.

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APPENDIX

The following persons and institutions, all in Australia, participated in the ACTS Study Group: *Steering group* — C.A. Crowther, R. Haslam, G.A. Dekker, J.S. Robinson; *Coordinating team* — C.A. Crowther, A.R. Rumbold, V. Coppinger, M. Vnuk, N. Thomas, J. Paynter, A. Brindley, E. Rosenfeld, S. Russell, C. Holst, K. Robinson; *Statistical support* — K. Willson; *Data monitoring committee:* J.E. Hiller, Y. Khong; *Writing group* — A.R. Rumbold, C.A. Crowther, R. Haslam, G.A. Dekker, J.S. Robinson; *Collaborating hospitals* (total number of women recruited at each hospital is in parentheses): Lyell McEwin Hospital, South Australia (188) — G. Dekker, N. Kretschmer, S. Agett, D. Wright, J. Dale. P. Duggan, S. Kennedy-Andrews; Mater Mother's Hospital, Queensland (500) — F.Y. Chan, V. Flenady, S. Jenkins-Manning, M. Jell, K. Waters, K. New, L. Lewis, J. McPhail, D. Karamujic, P. Gray; Modbury Hospital, South Australia (101) — J. Sieben, G. Matthews, M. Morton, L. Purins; Queen Elizabeth Hospital, South Australia (89) — B. Pridmore (deceased), L. Purins, M. Hoby, M. Sladek, J. Miller; Royal Brisbane Women's Hospital, Queensland (138) — P. Colditz, V. Smith-Orr, T. Fitzsimmons, M. Pritchard, C. Moroney, M. Wilson; Royal North Shore Hospital, New South Wales (131) — J. Morris, J. Milligan; Royal Women's Hospital, Melbourne, Victoria (146) — L. Kornman, F. Agresta, M. Stewart, M. Cram; Townsville Hospital, Queensland (85) — D. Watson, A. Lawrence, A. Dederer, E. Green; Women's and Children's Hospital, South Australia (499) — C.A. Crowther, J.S. Robinson, R.R. Haslam, A.R. Rumbold, S. Rogers, R. Sweet, M. Vnuk, N. Kretchsmer, L. Purins, L. Pirc, A. Brindley.

REFERENCES

1. ACOG Committee on Practice Bulletins–Obstetrics. ACOG practice bulletin: diagnosis and management of pre-eclampsia and eclampsia: number 33, January 2002. Obstet Gynecol 2002;99:159-67.
2. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 2000;183:S1-S22.
3. Slater EK, Sullivan EA, King JF. Maternal deaths in Australia 1997-1999. Maternal Deaths Series No. 1. Sydney: AIHW National Perinatal Statistics Unit, 2004. (AIHW cat. no. PER 24.) (Accessed March 31, 2006, at http://www.npsu.unsw.edu.au/md1high.htm.)
4. Kramer MS, Seguin L, Lydon J, Goulet L. Socio-economic disparities in pregnancy outcome: why do the poor fare so poorly? Paediatr Perinat Epidemiol 2000; 14:194-210.
5. Maternal, perinatal and infant mortality in South Australia 2002. Adelaide, Australia: Department of Human Services, 2003.
6. Khong TY, De Wolf F, Robertson WB, Brosens I. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. Br J Obstet Gynaecol 1986;93:1049-59.
7. Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet 1993;341:1447-51. [Erratum, Lancet 1993;342:504.]
8. Sacks GP, Studena L, Sargent K, Redman CW. Normal pregnancy and pre-eclampsia both produce inflammatory changes in peripheral blood leucocytes akin to those of sepsis. Am J Obstet Gynecol 1998;179:80-6.
9. Wickens D, Wilkins MH, Lunec J, Ball G, Dormandy TL. Free radical oxidation (peroxidation) products in plasma in normal and abnormal pregnancy. Ann Clin Biochem 1981;18:158-62.
10. Hubel CA, McLaughlin MK, Evans RW, Hauth BA, Sims CJ, Roberts JM. Fasting serum triglycerides, free fatty acids, and malondialdehyde are increased in preeclampsia, are positively correlated, and decrease within 48 hours post partum. Am J Obstet Gynecol 1996;174:975-82.
11. Mikhail MS, Anyaegbunam A, Garfinkel D, Palan PR, Basu J, Romney SL. Preeclampsia and antioxidant nutrients: decreased plasma levels of reduced ascorbic acid, alpha-tocopherol, and beta-carotene in women with preeclampsia. Am J Obstet Gynecol 1994;171:150-7.
12. Saugstad OD. Hypoxanthine as an indicator of hypoxia: its role in health and disease through free radical production. Pediatr Res 1988;23:143-50.
13. *Idem.* Update on oxygen radical dis-

ease in neonatology. Curr Opin Obstet Gynecol 2001;13:147-53.
14. Chappell LC, Seed PT, Briley AL, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. Lancet 1999;354:810-6.
15. Beazley D, Ahokas R, Livinston J, Griggs M, Sibai BM. Vitamin C and E supplementation in women at high risk of pre-eclampsia: a double-blind placebo-controlled trial. Am J Obstet Gynecol 2005;192:520-1.
16. Corrigan JJ Jr, Ulfers LL. Effect of vitamin E on prothrombin levels in warfarin-induced vitamin K deficiency. Am J Clin Nutr 1981;34:1701-5.
17. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust N Z J Obstet Gynaecol 2000;40:139-55.
18. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.
19. Donoghue DA, Cust AC. The Australian and New Zealand Neonatal Network 1998. Neonatal Network series. No. 4. Sydney: AIHW National Perinatal Statistics Unit, 2000. (AIHW cat. No. PER 13.)
20. Hannah ME, Hannah WJ, Hellmann J, Hewson S, Milner R, William A. Induction of labor as compared with serial antenatal monitoring in post-term pregnancy: a randomized controlled trial. N Engl J Med 1992;326:1587-92. [Erratum, N Engl J Med 1992;327:368.]
21. Roberts CL, Lancaster PAL. Australian national birthweight percentiles by gestational age. Med J Aust 1999;170:114-8.
22. Hochberg Y, Tamhane AC. Multiple comparison procedures. New York: John Wiley, 1987.
23. Crowther CA, Hiller JE, Pridmore B, et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial. Aust N Z J Obstet Gynaecol 1999;39:12-8.
24. Recommended dietary intakes. In: Recommended daily allowances (RDA), 10th ed. Washington, D.C.: National Academy of Sciences, 1989. (Accessed March 31, 2006, at http://www.nal.usda.gov/fnic/dga/rda.pdf.)
25. Carr A, Frei B. Does vitamin C act as a pro-oxidant under physiological conditions? FASEB J 1999;13:1007-24.
26. Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. N Engl J Med 1997;337:69-76.
27. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A 1996;93:3704-9.
28. Devaraj S, Adams-Huet B, Fuller CJ, Jialal I. Dose response comparison of RRR-alpha-tocopherol and all-racemic alpha-tocopherol on LDL oxidation. Arterioscler Thromb Vasc Biol 1997;17:2273-9.
29. Rumbold A, Duley L, Crowther C, Haslam R. Antioxidants for preventing pre-eclampsia. Cochrane Database Syst Rev 2005;4:CD004227.
30. Bendich A, Machlin LJ. The safety of oral intake of vitamin E: data from clinical studies from 1986 to 1991. In: Packer L, Fuchs J, eds. Vitamin E in health and disease. New York: Marcel Dekker, 1993:411-6.
31. Poston L, Shennan A. Vitamins in Pre-eclampsia trial. (Accessed March 31, 2006, at http://www.medscinet.com/vip/.)
32. Roberts JM, National Institute of Child Health and Human Development, Maternal Fetal Medicine Units Network. Combined Antioxidant and Preeclampsia Prediction Studies (CAPPS). (Accessed March 31, 2006, at http://www.clinicaltrials.gov/ct/show/NCT00135707?order=7.)
33. Fraser WD, Audibert F, Bujold E, et al. The vitamin E debate: implications for ongoing trials of pre-eclampsia prevention. BJOG 2005;112:684-8.
34. Holmes VA, Young IS, Maresh MJ, Pearson DW, Walker JD, McCance DR. The Diabetes and Pre-eclampsia Intervention Trial. Int J Gynaecol Obstet 2004;87:66-71.
35. Spinnato JA. Antioxidant therapy to prevent preeclampsia. (Accessed March 31, 2006, at http://www.clinicaltrials.gov/ct/show/NCT00097110?order=9.)

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