# Vitamin E: maternal concentrations are associated with fetal growth[1–3]

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**ABSTRACT**

**Background:** Few data exist on the effects of the 2 most abundant isomers of vitamin E ($\alpha$- and $\gamma$-tocopherols) on fetal growth.

**Objective:** We measured maternal plasma concentrations of $\alpha$- and $\gamma$-tocopherols and examined their relation with measures of fetal growth. We also examined the relation, controlled for associated maternal factors, of diet and supplement use to tocopherol concentrations at week 28 of gestation.

**Design:** A cohort of 1231 gravid women from Camden, NJ, was studied from entry to care (16.0 $\pm$ 0.15 wk gestation); plasma tocopherol concentrations were measured at entry and at week 28.

**Results:** Plasma concentrations of $\alpha$-tocopherol at entry and at week 28 were positively related to increased fetal growth (birth weight for gestation), a decreased risk of small-for-gestational-age births, and an increased risk of large-for-gestational-age births. Concentration of $\alpha$-tocopherol at week 28 was positively related to use of prenatal multivitamins and dietary intake of vitamin E; concentration of $\gamma$-tocopherol was related positively to dietary fat intake and negatively to multivitamin use.

**Conclusion:** Early and late circulating concentrations of $\alpha$-tocopherol are positively associated with fetal growth. *Am J Clin Nutr* 2006;84:1442–8.

**KEY WORDS** Birth weight, fetal growth, small for gestational age, large for gestational age, vitamin E, antioxidants, $\gamma$-tocopherol, $\alpha$-tocopherol, multivitamins, maternal nutrition, pregnancy

## INTRODUCTION

Emerging evidence suggests that during pregnancy oxidative damage to DNA, protein, and lipids may be associated with reduced birth weight and increased risks of outcomes such as low birth weight, preterm delivery, and preeclampsia (1–3). Risk may, however, depend on the mother's antioxidant status (1, 3) which potentially protects the maternal-fetal unit, thus increasing intrauterine growth and infant weight at birth.

Antioxidants scavenge free radicals and buffer the effects of prooxidants by reducing oxidative stress and preventing oxidative damage. Antioxidants are produced endogenously by the body or are consumed as part of the diet. Vitamin E is a lipid-soluble chain-breaking antioxidant that is dietary in origin. Of the 8 isomers of vitamin E that occur naturally, $\alpha$-tocopherol is the most abundant in plasma, cell membranes, other human tissues, and nutritional supplements, whereas $\gamma$-tocopherol is the primary form found in the human diet. The concentration of $\gamma$-tocopherol in plasma and tissues is 4–5-fold lower than $\alpha$-tocopherol (4).

In addition to its antioxidant actions, an effect of vitamin E that is of potential consequence for the course and outcome of pregnancy involves prostacyclin (4). Vitamin E enhances the release of prostacyclin, a metabolite of arachadonic acid that inhibits platelet aggregation, quiets uterine contractility, and increases vasodilation (4). Thus, it is plausible that circulating concentrations of $\alpha$- and $\gamma$-tocopherols could be associated with altered fetal growth by increased blood flow and nutrient supply to the fetus.

The influence of $\alpha$-tocopherol on fetal growth has been examined only rarely; as far as we are aware, effects of $\gamma$-tocopherol are unstudied. We therefore investigated the relation of the 2 most plentiful isomers of vitamin E, $\alpha$- and $\gamma$-tocopherols, with birth weight for gestational age and other indexes of fetal growth.

## SUBJECTS AND METHODS

The Camden Study (2, 3, 5, 6) examines prospectively the effects of maternal nutrition and growth in generally healthy pregnant women from one of the poorest cities in the United States. Participants include young ($\leq$18 y) and more mature (19–45 y) women enrolling for prenatal care in Camden, NJ, clinics. Gravid women with serious nonobstetric problems (eg, lupus, chronic hypertension, diabetes mellitus type 1 or type 2, seizure disorders, malignancies, and drug or alcohol abuse) were not eligible. The Institutional Review Board of the University of Medicine and Dentistry of New Jersey, School of Osteopathic Medicine approved the study. In this analysis, we focus on data from 1231 gravid women who enrolled in the study between January 1998 and April 2005.

Socioeconomic, demographic, lifestyle, and dietary data were obtained by interview at entry to prenatal care and updated at week 20 and week 28 of gestation. A 24-h recall of the previous day's diet was obtained on the same schedule, processed with databases from the Campbell Institute of Research and Technology (Campbell Soup Company) in Camden, NJ, and nutrient

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values were averaged across the pregnancy. The database generates data for >70 nutrients with the use of the US Department of Agriculture's Nutrient Database for Standard Reference (Release 13, 2000; http://www.nal.usda.gov/fnic/foodcomp), the Continuing Survey of Food Intakes by Individuals (http://www.barc.usda.gov/bhnrc/foodsurvey/), and data from the scientific literature.

Pregravid weight was determined by recall at entry to prenatal care, and weight was measured at each visit with the use of a beam balance scale. Height was measured at entry with the use of a stadiometer. Body mass index (BMI; in kg/m$^2$) was computed with pregravid weight and height. Information on current and past pregnancy outcomes, complications, and infant abnormalities was abstracted from the prenatal record, the delivery record, delivery logbooks, and the infant's chart. Large for gestational age was defined by a birth weight above the 90th percentile of Zhang's standard that adjusts for maternal parity, ethnicity, and fetal sex (7). Small for gestational age was defined by birth weight below the 10th percentile of the same standard. Gestation duration was based on the gravid woman's last normal menstrual period confirmed or modified by ultrasound scan.

Samples of the mother's blood were obtained at entry to care and at 28 wk gestation, processed, and stored at −80 °C for up to 3 y before analysis. Three independent groups (from the National Institute of Standards and Technology, Center for Public Health Research, and Dartmouth Medical School) have shown that vitamin E ($\alpha$- and $\gamma$-tocopherols) is stable at this temperature for periods of ≥4 y (8–11). Vitamin E was measured by HPLC with the use of the method of Bieri et al (12). Standard compounds were obtained from Sigma Diagnostics (St. Louis, MO), and 100 $\mu$L plasma was used for each test. The within-assay CVs were 1.0% and 0.8% for $\alpha$- and $\gamma$-tocopherol, respectively, and the between-assay CVs were 8% for both. Cholesterol was determined by the Lieberman-Burchardt method with the use of a kit marketed by Pointe Scientific (Canton, MI). The within-assay CV was 2.0%, the between-assay CV was 2.7%.

Linear regression was used to adjust plasma concentrations of $\alpha$- and $\gamma$-tocopherols at entry for the exact week in gestation when the sample was drawn, to adjust vitamin E and total fat intakes for energy, and to adjust birth weight for gestation duration to index fetal growth. Because the tocopherols are fat soluble and transported in the bloodstream by plasma lipoproteins, we also used regression to adjust both isomers for total cholesterol (4).

The significance of the linear trend of $\alpha$- and $\gamma$-tocopherols across categories of maternal characteristics was assessed with the use of analysis of variance, chi-square test, and *t* test. The *P* values from any pairwise contrasts that followed analysis of variance were Bonferroni corrected to adjust for multiple comparisons. Multiple linear regression was used to examine associations between circulating concentrations of the tocopherols at week 28 with the maternal diet (vitamin E and dietary fat) and with the use of prenatal multivitamin and mineral supplements. We also tested for differences that timing and frequency of multivitamin use had on circulating concentrations of $\alpha$-tocopherol by comparing coefficients for multivitamin use before pregnancy, at entry to care, and at week 28 with one another (PROC REG; SAS Institute, Cary, NC).

Potential confounding variables traditionally associated with infant birth weight and fetal growth (eg, age, smoking, ethnicity, BMI) which are also associated with the concentrations of $\alpha$- and $\gamma$-tocopherols were included in multivariable models. Separate models were fit for pregnancy outcomes of interest, including fetal growth (birth weight adjusted for gestation), and births that were small or large for gestational age with the use of multiple logistic or multiple linear regression (13). Confounding was assessed by comparing crude and adjusted odds ratios or regression coefficients with and without additional adjustment for cholesterol. Adjusted odds ratios and their 95% CIs were computed from the logistic regression coefficients and their corresponding covariance matrixes (13). Data were analyzed with SAS version 9.0 (SAS Institute). Because both cholesterol-adjusted and -unadjusted data gave similar results, the cholesterol-adjusted data are presented.

## RESULTS

The cohort of 1231 pregnant women had a mean age of 22.9 ± 5.2 y ($\bar{x}$ ± SEM). Most were Hispanic (49.1%) or African American (39.7%). Gestation at entry was 16.0 ± 0.15 wk. Gestation duration averaged 38.4 ± 0.075 wk; mean birth weight was 3170 ± 17.69 g.

**TABLE 1**
Concentrations of $\alpha$- and $\gamma$-tocopherol and maternal characteristics at entry[1]

| | | Mean concentration[1] | |
|---|---|---|---|
| Maternal characteristics | *n* | $\alpha$-Tocopherol | $\gamma$-Tocopherol |
| | | *μg/mL* | |
| Maternal age (y) | | | |
| ≤16 | 67 | 10.22 ± 0.33[2] | 1.77 ± 0.08[3] |
| 16.1–19.0 | 309 | 11.12 ± 0.16 | 1.82 ± 0.04 |
| 19.1–29.0 | 711 | 11.37 ± 0.10 | 1.96 ± 0.02 |
| 29.1–39.0 | 139 | 12.40 ± 0.23 | 1.99 ± 0.05 |
| >39.0 | 5 | 13.34 ± 1.22 | 2.18 ± 0.29 |
| Parity | | | |
| Parous | 770 | 11.35 ± 0.10 | 1.99 ± 0.02[2] |
| Nulliparous | 461 | 11.41 ± 0.11 | 1.81 ± 0.03 |
| BMI (kg/m$^2$) | | | |
| ≤19.8 | 150 | 11.40 ± 0.23[4] | 1.85 ± 0.05[2] |
| 19.9–26.0 | 583 | 11.51 ± 0.11 | 1.81 ± 0.03 |
| 26.1–29.0 | 175 | 11.62 ± 0.21 | 1.93 ± 0.05 |
| >29.0 | 323 | 10.99 ± 0.15 | 2.15 ± 0.04 |
| Ethnicity | | | |
| Hispanic | 604 | 11.66 ± 0.11[2] | 1.83 ± 0.03[2] |
| African American | 439 | 10.76 ± 0.13 | 2.02 ± 0.03 |
| White | 177 | 11.82 ± 0.21 | 2.00 ± 0.05 |
| Asian and other | 11 | 13.19 ± 0.86 | 1.84 ± 0.21 |
| Cigarettes smoked/d | | | |
| None | 1065 | 11.40 ± 0.08 | 1.91 ± 0.02 |
| 1–9 | 109 | 11.30 ± 0.27 | 1.96 ± 0.06 |
| ≥10 | 57 | 11.00 ± 0.37 | 2.05 ± 0.09 |
| Concentration at entry | 1231 | 11.37 ± 0.07[5] | 1.92 ± 0.02[6] |
| Concentration at week 28 | 1204 | 13.70 ± 0.10 | 2.11 ± 0.02 |

[1] All values are $\bar{x}$ ± SEM. Concentrations were adjusted for gestation at entry.
[2] *P* for trend < 0.0001 (ANOVA).
[3] *P* for trend <0.01 (ANOVA).
[4] *P* for trend < 0.05 (ANOVA).
[5] $\alpha$-Tocopherol concentration at entry was significantly different from that at week 28, *P* < 0.0001 (*t* test).
[6] $\gamma$-Tocopherol concentration at entry was significantly different from that at week 28, *P* < 0.0001 (*t* test).

**TABLE 2**
Multiple regression analysis of maternal characteristics, diet, and supplement use as predictors of α- and γ-tocopherol concentrations at week 28[1]

| | | α-Tocopherol[2] | | γ-Tocopherol[2] | |
|---|---|---|---|---|---|
| | *n* | Regression coefficient ± SE | 95% CI | Regression coefficient ± SE | 95% CI |
| | | *μg/mL* | | *μg/mL* | |
| Maternal characteristic | | | | | |
| Age (y) | 1204 | 0.163 ± 0.0198[3] | 0.124, 0.202 | −0.0017 ± 0.005 | −0.011, 0.007 |
| BMI (kg/m$^2$) | 1204 | −0.068 ± 0.0143[3] | −0.096, −0.040 | 0.0181 ± 0.0034[3] | 0.0116, 0.025 |
| Nulliparous | 453 | 0.714 ± 0.207[4] | 0.308, 1.120 | −0.131 ± 0.048[5] | −0.226, −0.035 |
| Parous | 751 | Reference | — | Reference | — |
| Cigarette smoker | 222 | −0.552 ± 0.236[6] | −1.014, −0.089 | −0.0244 ± 0.055 | −0.133, 0.084 |
| Nonsmoker | 982 | Reference | — | Reference | — |
| Hispanic | 580 | −0.870 ± 0.269[5] | −1.398, −0.342 | −0.282 ± 0.063[3] | −0.405, −0.158 |
| African American | 441 | −1.683 ± 0.280[3] | −2.232, −1.134 | −0.106 ± 0.065 | −0.235, 0.022 |
| White and other | 183 | Reference | — | Reference | — |
| *P* for ethnicity | | < 0.001 | | < 0.001 | |
| Supplement use | | | | | |
| Before pregnancy | | | | | |
| Use | 159 | 0.624 ± 0.267[6] | 0.099, 1.148 | −0.067 ± 0.063 | −0.19, 0.055 |
| No Use | 1045 | Reference | — | Reference | — |
| At entry | | | | | |
| Daily use | 765 | 0.421 ± 0.211[6] | 0.006, 0.836 | −0.0095 ± 0.05 | −0.107, 0.088 |
| Less than daily use | 124 | 0.143 ± 0.331 | −0.506, 0.792 | −0.017 ± 0.08 | −0.169, 0.135 |
| No use | 315 | Reference | — | Reference | — |
| *P* for trend | | < 0.05 | | 0.83 | |
| At week 28 | | | | | |
| Daily use | 846 | 0.966 ± 0.254[3] | 0.468, 1.464 | −0.292 ± 0.06[3] | −0.409, −0.176 |
| Less than daily use | 168 | 0.452 ± 0.330 | −0.196, 1.10 | −0.323 ± 0.08[3] | −0.475, −0.171 |
| No use | 190 | Reference | — | Reference | — |
| *P* for trend | | < 0.001 | | < 0.001 | |
| Vitamin E intake (mg α-TE/d)[7,8] | 1204 | 0.054 ± 0.025[6] | 0.005, 0.104 | −0.011 ± 0.006 | −0.022, 0.001 |
| Total fat intake (g/d)[7,8] | 1204 | −0.002 ± 0.005 | −0.012, 0.008 | 0.003 ± 0.001[5] | 0.0002, 0.005 |

[1] α-TE, α-tocopherol equivalent.
[2] Concentrations of α- and γ-tocopherol are adjusted for total plasma cholesterol.
[3] $P < 0.0001$.
[4] $P < 0.001$.
[5] $P < 0.01$.
[6] $P < 0.05$.
[7] Adjusted for energy intake.
[8] $\bar{x}$ intake ± SEM for vitamin E: 7.19 ± 0.13 mg α-TE; total fat: 84.2 ± 1.0 g; energy: 2203 ± 19.8 kcal.

Descriptive data for the cohort at entry, including plasma concentrations of α- and γ-tocopherols at entry and at week 28, are given in **Table 1**. Associations were detected between the tocopherol isomers and several maternal factors. Women with the highest circulating concentrations of either α- or γ-tocopherol were somewhat older and, for γ-tocopherol, were more likely to be parous and to have a higher BMI (Table 1). Obese women (BMI > 29) had significantly lower concentrations of α-tocopherol (obese: 10.99 ± 0.15 μg/mL; nonobese: 11.51 ± 0.09 μg/mL; $P < 0.01$, *t* test) and significantly higher concentrations of γ-tocopherol (obese: 2.15 ± 0.04 μg/mL; nonobese: 1.84 ± 0.02 μg/mL; $P < 0.0001$) than did the nonobese women. Significant ethnic differences were present (*t* test with Bonferroni's correction). African Americans had lower concentrations of α-tocopherol than did Hispanics, whites, or Asians (all $P < 0.05$); whereas Hispanics had lower concentrations of γ-tocopherol than did African American and white gravid women (all $P < 0.05$). Concentrations of both isomers increased significantly ($P < 0.0001$) between entry and week 28 gestation, rising by 20.5% (α-tocopherol: 11.37 compared with 13.70 μg/mL) and 9.9% (γ-tocopherol: 1.92 compared with 2.11 μg/mL), respectively (Table 1).

As indicated in **Table 2**, at week 28 concentrations of α-tocopherol (cholesterol adjusted) decreased with increasing BMI and were lower in smokers and in Hispanic and African American women. Concentrations of α-tocopherol rose with increasing maternal age and intake of Vitamin E from diet; concentrations also were higher in nulliparous women and in women who used prenatal multivitamins (Table 2). In comparison to gravid women not using multivitamins, daily use by week 28 increased circulating concentrations of α-tocopherol by 0.966 μg/mL; daily use of prenatal multivitamins at entry or before pregnancy had similar effects to use at week 28. No significant differences were observed in the concentration of α-tocopherol when coefficients for daily multivitamin use by week 28, daily use at entry, or use before pregnancy were compared. Vitamin E from diet (energy adjusted) also was associated with increased circulating concentrations such that a gravid

**TABLE 3**
Concentration of α-tocopherol by quintile (Q) and birth weight for gestation[1]

| | | Birth weight[2] | |
|---|---|---|---|
| | *n* | Unadjusted | Adjusted |
| | | *g* | |
| At entry[3] | | | |
| Q1 | 246 | 3144 ± 40[4] | 3105 ± 28 |
| Q2 | 246 | 3177 ± 40 | 3174 ± 27 |
| Q3 | 246 | 3186 ± 40 | 3199 ± 27 |
| Q4 | 247 | 3102 ± 40 | 3150 ± 27 |
| Q5 | 246 | 3242 ± 40 | 3221 ± 29 |
| At week 28[5] | | | |
| Q1 | 240 | 3171 ± 35 | 3156 ± 29 |
| Q2 | 242 | 3184 ± 35 | 3224 ± 27 |
| Q3 | 240 | 3242 ± 35 | 3241 ± 27 |
| Q4 | 241 | 3224 ± 35 | 3231 ± 27 |
| Q5 | 241 | 3340 ± 35 | 3314 ± 30 |

[1] A test for differences between models for effects of tocopherol at entry and at week 28 on birth weight showed no difference between times; $P < 0.0001$ for effect of α-tocopherol with both points combined.

[2] Models were adjusted for age, parity, prepregnant BMI, ethnicity, smoking, energy intake, and gestation duration. Entry model was also adjusted for gestation at entry; α-tocopherol was adjusted for total plasma cholesterol.

[3] Concentration of α-tocopherol for Q1 is ≤9.06 μg/mL, Q2 is 9.07–10.40 μg/mL, Q3 is 10.41–11.61 μg/mL, Q4 is 11.62–13.34 μg/mL, and Q5 is >13.34 μg/mL.

[4] $\bar{x}$ ± SEM (all such values).

[5] Concentration of α-tocopherol for Q1 is ≤10.84 μg/mL, Q2 is 10.85–12.45 μg/mL, Q3 is 12.46–14.00 μg/mL, Q4 is 14.01–15.98 μg/mL, and Q5 is >15.98 μg/mL.

**TABLE 4**
Concentration of α-tocopherol by quintile (Q) and small-for-gestational-age (SGA) births[1]

| | *n* | Unadjusted % of SGA | Adjusted odds ratio | 95% CI |
|---|---|---|---|---|
| At entry[2] | | | | |
| Q1 | 246 | 7.76 | 1.00 | — |
| Q2 | 246 | 7.76 | 1.00 | 0.51, 1.95 |
| Q3 | 246 | 5.31 | 0.62 | 0.39, 1.33 |
| Q4 | 247 | 9.02 | 1.09 | 0.57, 2.09 |
| Q5 | 246 | 6.10 | 0.66 | 0.32, 1.36 |
| At week 28[3] | | | | |
| Q1 | 240 | 8.37 | 1.00 | — |
| Q2 | 242 | 8.26 | 0.92 | 0.47, 1.80 |
| Q3 | 240 | 4.58 | 0.51 | 0.22, 1.12 |
| Q4 | 241 | 8.71 | 0.96 | 0.48, 1.92 |
| Q5 | 241 | 3.73 | 0.34 | 0.13, 0.87 |

[1] SGA birth defined by Zhang's standard (7) that adjusts for maternal parity, ethnicity, and fetal sex. Models were also adjusted for age, BMI, smoking, and energy intake. α-Tocopherol was adjusted for total plasma cholesterol. A test for differences between models for effects of α-tocopherol at entry and at week 28 on risk of SGA birth showed no difference between times; $P = 0.03$ for the effect of α-tocopherol with both points combined.

[2] Concentration of α-tocopherol for Q1 was ≤9.06 μg/mL, Q2 was 9.07–10.40 μg/mL, Q3 was 10.41–11.61 μg/mL, Q4 was 11.62–13.34 μg/mL, and Q5 was >13.34 μg/mL.

[3] Concentration of α-tocopherol for Q1 was ≤10.84 μg/mL, Q2 was 10.85–12.25 μg/mL, Q3 was 12.46–14.00 μg/mL, Q4 was 14.01–15.98 μg/mL, and Q5 was >15.98 μg/mL.

woman who consumed vitamin E at the recommended daily allowance (15 mg α-tocopherol equivalents/d) would have circulating concentrations of α-tocopherol 0.42 μg/mL higher than a gravid woman with vitamin E intake at the mean (± SE) for the cohort (7.19 ± 0.13 mg α-tocopherol equivalents/d). γ-Tocopherol showed relations with diet and multivitamin use that differed from α-tocopherol in that daily and less than daily use at week 28 was associated with significantly lower concentrations, as were parity and Hispanic ethnicity (Table 2). No association with multivitamin use before pregnancy or at entry was apparent. Total fat intake (energy adjusted) and BMI each had a positive and significant relation to γ-tocopherol, whereas vitamin E from diet was unrelated.

The association between α-tocopherol and birth weight for gestation was observed both at entry and at week 28 of gestation. After adjustment for age, parity, BMI, ethnicity, smoking, and gestation duration, and when examined by quintile, significant linear trends were observed for birth weight to increase as the quintile of α-tocopherol concentration increased (**Table 3**). At entry, a birth weight difference of 116 g was observed between the highest and lowest quintiles of α-tocopherol concentration; the difference was 158 g when the same comparison was made at week 28. When examined as a continuous variable, after controlling for the same confounding variables, cholesterol-adjusted concentration of α-tocopherol showed a linear relation with birth weight. At entry this amounted to an increase of 11.84 ± 4.91 g birth weight per microgram of α-tocopherol per milliliter ($P < 0.05$, multiple regression), and at week 28 the increase was 16.22 ± 4.02 g birth weight per microgram of α-tocopherol per milliliter ($P < 0.001$). Unlike α-tocopherol, γ-tocopherol showed no association with birth weight for gestation. The difference between extreme quintiles amounted to 19 g at entry and 8 g at week 28; neither was statistically significant.

A high plasma concentration of α-tocopherol at week 28 was associated with nearly a 3-fold reduction in risk of bearing a small-for-gestational age (SGA) infant when highest and lowest quintiles were compared, the *P* for trend across the quintiles ($P < 0.05$) also was statistically significant (**Table 4**). Consistent with this, the concentration of α-tocopherol was significantly lower at week 28 when data from women who delivered an SGA infant were compared with women who did not deliver an SGA infant (SGA infant: 12.95 ± 0.35 μg α-tocopherol/mL; no SGA infant: 13.73 ± 0.09; $P < 0.05$, *t* test). None of the gravid women delivering an SGA infant had gestational diabetes. At entry no difference in the concentration of α-tocopherol was associated with an SGA infant.

A total of 6.17% ($n = 76$) infants born to women in the cohort were large for gestational age. The relation between maternal concentration of α-tocopherol and the risk of a large-for-gestational age (LGA) infant was detectable at entry and at week 28. The mean concentration of α-tocopherol was significantly higher at both points when women with subsequent LGA infants ($n = 76$) were compared with the others [at entry: 12.1 ± 0.32 μg α-tocopherol/mL (LGA infant) compared with 11.33 ± 0.08 μg α-tocopherol/mL (not LGA infant); $P < 0.01$, *t* test; at week 28: 14.87 ± 0.41 μg α-tocopherol/mL (LGA infant) compared with 13.58 ± 0.11 μg α-tocopherol/mL (not LGA infant); $P < 0.05$]. When examined in multiple logistic regression (**Table 5**), with the use of α-tocopherol as a continuous variable, the odds for

**TABLE 5**
Maximum likelihood estimates of logistic parameters relating α-tocopherol concentrations to risk of large-for-gestational-age (LGA) births[1]

| | *n* | Logistic regression coefficient | SE | Adjusted odds ratio | 95% CI |
|---|---|---|---|---|---|
| α-Tocopherol[2] | | | | | |
| Entry | 1231 | 0.085 | 0.04 | 1.09 | 1.01, 1.18 |
| Week 28 | 1204 | 0.065 | 0.031 | 1.07 | 1.00, 1.13 |

[1] LGA birth defined as weight >90th percentile by Zhang's standard (7) that adjusts for maternal ethnicity, parity, and fetal sex. Models were also adjusted for age, BMI, and smoking. There were 76 LGA infants.

[2] α-Tocopherol concentrations (in μg/mL) were adjusted for cholesterol. Entry α-tocopherol concentration was also adjusted for gestation at entry. A test for differences between models for effects of tocopherol at entry and at week 28 on risk of LGA birth showed no difference between times; $P = 0.004$ for the effect of α-tocopherol with both points combined.

bearing an LGA infant increased by 8.8% at entry and 6.7% at week 28 for each unit (in μg/mL) increase in the concentration of α-tocopherol. Thus, by our calculation, risk of bearing an LGA infant approximately doubled between the highest and lowest quintiles of α-tocopherol concentration. Adjustment for maternal obesity (compared with nonobesity) in lieu of BMI and inclusion of gestational diabetes (presence or absence) in models for LGA infants did little to alter these results. γ-Tocopherol concentrations at entry or at week 28 were not associated with risk of bearing an LGA or an SGA infant.

## DISCUSSION

Vitamin E is a nutrient that has both antioxidant and nonantioxidant properties. As an antioxidant it inhibits oxidation of LDL cholesterol, scavenges free radicals, and prevents the propagation of lipid peroxides. Among the nonantioxidant properties of vitamin E is the up-regulation of prostacyclin, a reduction in inflammation, and a decrease in the production of cellular adhesion molecules (4). Because of these properties, vitamin E has been linked to the prevention of chronic disease and, in particular, ischemic heart disease. The form of the vitamin examined in observational studies and administered in the largely ineffective randomized trials for chronic disease prevention has been α-tocopherol (4, 14, 15).

The present study is the first large-scale epidemiologic examination of circulating concentrations of α-tocopherol and γ-tocopherol during pregnancy. Adding to its import is that the study was carried out in a vulnerable population. Camden, NJ, is a poor city, one of the poorest in the United States, and >85% of the participants are minorities. We have previously documented multiple problems that include a nutritional component in this population, and several have an adverse influence on pregnancy course and outcome (3, 5, 6, 16–18). Use of prenatal multivitamins by gravid women in Camden is associated with a reduction in several of these risks (19).

Consistent with prior reports on vitamin E (20, 21), the concentration of both α- and γ-tocopherols increased with gestation. At both entry and week 28, we found that higher circulating concentrations of α-tocopherol were positively associated with several indicators of fetal growth. These indicators included increased birth weight for gestation, an increased risk of the birth of infants that were large for gestational age, and a reduced risk of the birth of infants that were small for gestational age. γ-Tocopherol was not associated with any of these indicators of fetal growth.

Few studies of the effects of maternal concentrations of vitamin E on pregnancy outcome have included fetal growth. More than a decade ago von Mandach et al (22) studied >300 women and their offspring and correlated lower concentrations of vitamin E at delivery with term low birth weight ($n = 12$), a measure of SGA infants. More recently, lower concentrations of vitamin E were found to be associated with a 2-fold increased risk of bearing an SGA infant in HIV-infected women from Tanzania (23). In addition, a prospective study of South Korean women reported a positive but not statistically significant relation between higher maternal concentrations of vitamin E during the second trimester and increased infant birth weight (24). Some studies, often of small sample size, have suggested the possibility of an association with fetal growth (25–27); others, however, have found no relation (28, 29). One recent study reported lower birth weights among infants born to women taking high doses of vitamin E supplements (>400 IU/d) (30). In that study control subjects were recruited from among women calling a hotline for advice about exposure to toxic agents and teratogens during pregnancy; their use of supplemental vitamin E was not ascertained. The method used to recruit women to use vitamin E supplements was never detailed; characteristics that potentially confound effects of supplement use on infant birth weight (eg, maternal ethnicity and parity) were neither reported nor controlled. Thus, vitamin E users and control subjects seem not to have been ascertained or studied with the same methods.

Consistent with data from the third National Health and Nutrition Examination Survey (NHANES III) (31) we observed that African Americans had the lowest concentrations of α-tocopherol of any ethnic group studied both at entry and at week 28. We also observed lower concentrations of α-tocopherol at week 28 among Hispanic gravid women. These observations are consistent with lower infant birth weights among African Americans and some Hispanic ethnic groups (Puerto Ricans) (32). At week 28, we found lower concentrations of α-tocopherol in smokers, which was also in agreement with results from the NHANES III (31) and consistent with the well-known difference in birth weight between smokers and nonsmokers.

We are aware of no study of pregnant women that also included γ-tocopherol, the principal isomer of vitamin E found in the human diet. γ-Tocopherol has an efficacy that is similar to or greater than α-tocopherol for quenching reactive oxygen species, but it is more effective against reactive nitrogen species (4, 33, 34). Lower circulating concentrations have been associated with an increased risk of cardiovascular disease (34), but this isomer has not been used in randomized trials. Metabolic studies showed faster plasma γ-tocopherol disappearance and increased γ-metabolite production compared with α-tocopherol which were more pronounced in women then in men (35). An α-tocopherol transfer protein found in the liver also maintains higher circulating concentrations by selectively incorporating α-tocopherol into plasma for dissemination (33, 34).

We also examined the relation of diet and supplement use to circulating concentrations of both tocopherol isomers. Both diet and multivitamin use were positively associated with increased

circulating concentration of α-tocopherol concentration. Consistent with findings from the NHANES III, concentrations of α-tocopherol were higher among multivitamin users (31). Prior studies reported little relation between dietary and circulating concentrations of vitamin E (4, 31). Supplements that contain α-tocopherol reduce circulating concentrations of γ-tocopherol (36). Our data also showed this effect. Concentrations of γ-tocopherol at week 28 were lower among women using multivitamins, all of which contain α-tocopherol. Although dietary intake of vitamin E showed little association, fat intake had a positive effect on plasma concentrations of γ-tocopherol that was statistically significant. Vitamin E is a fat-soluble vitamin, and its relation to fat intake is well described (4).

Vitamin E enhances the release of prostacyclin (4). During pregnancy, the vasodilatory effects of prostacyclin include regulation of blood flow between placenta and fetus and within the fetal circulation (21, 37–39). In preeclampsia, an imbalance between prostacyclin and thromboxane is associated with vasoconstriction; reduced blood flow between fetus and placenta is thought to increase the risk of fetal growth restriction (37–39). However, in a clinical trial to prevent preeclampsia, giving high doses of 2 antioxidants (vitamins C and E) to high-risk women reduced the risk of preeclampsia but did not increase fetal growth (1). A recent multicenter trial ($n = 2410$) showed that prophylactic supplementation with the same regimen (400 IU vitamin E, 1000 mg vitamin C) not only failed to reduce the risk of preeclampsia but also increased the risk of delivering an infant with low birth weight (<2500 g). However, increased infant birth weight (measured as birth weight centiles) was associated with use of prenatal multivitamins for women in the placebo arm of that trial (40).

In summary, our results suggest that α-tocopherol is positively associated with fetal growth. It is plausible that circulating concentrations of α-tocopherol could be associated with some increase in fetal growth by greater blood flow and nutrient supply to the fetus. It is equally plausible that α-tocopherol might be a biomarker for other maternal factors that are more directly involved in the causal pathway to fetal growth.

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## REFERENCES

1. Chappell LC, Seed PT, Briley A, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomized trial. Lancet 1999;354:810–6.
2. Scholl TO, Stein TP. Oxidant damage to DNA and pregnancy outcome. J Matern Fetal Med 2001;10:182–5.
3. Scholl TO, Leskiw M, Chen X, Sims M, Stein TP. Oxidative stress, diet and the etiology of preeclampsia. Am J Clin Nutr 2005;81:1390–6.
4. Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium and carotenoids. Washington, DC: National Academy Press, 2000.
5. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. Am J Clin Nutr 2005;81(suppl):1218S–22S.
6. Scholl TO, Chen X, Khoo CS, Lenders C. The dietary glycemic index during pregnancy: influence on infant birth weight, fetal growth and biomarkers of carbohydrate metabolism. Am J Epidemiol 2004;159:467–74.
7. Zhang J, Bowes WA. Birth-weight-for-gestational-age patterns by race, sex and parity in the United States population. Obstet Gynecol 1995;86:200–8.
8. Brown TJ, Duewer DL, Kline MC, Sharpless KE. The stability of retinol, alpha-tocopherol, trans-lycopene, and trans-beta-carotene in liquid-frozen and lyophilized serum. Clinica Chimica Acta 1998;276:75–87.
9. Comstock GW, Norkus EP, Hoffman SC, Xu MW, Helzlsouer KJ. Institution stability of ascorbic acid, carotenoids, retinol, and tocopherols in plasma stored at −70 degrees C for 4 years. Cancer Epidemiol Biomarkers Prev 1995;4:505–7.
10. Comstock GW, Alberg AJ, Helzlsouer KJ. Reported effects of long-term freezer storage on concentrations of retinol, beta-carotene, and alpha-tocopherol in serum or plasma summarized. Clin Chem 1993;39:1075–8.
11. Edmonds BK, Nierenberg DW. Serum concentrations of retinol, d-alpha-tocopherol and beta-carotene: effects of storage at −70 degrees C for five years. J Chromatogr 1993;614:169–74.
12. Bieri JG, Tolliver TJ, Catignani GL. Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromatography. Am J Clin Nutr 1979;32:2143–9.
13. Schlesselman JJ. Case-control studies. New York, NY: Oxford University Press, 1982.
14. Traber MG. Does vitamin E decrease heart attack risk? Summary and implications with respect to dietary recommendations. J Nutr 2001;131(suppl):395S–7S.
15. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer. JAMA 2005;294:56–65.
16. Scholl TO, Hediger ML, Schall JI, Khoo CS, Fischer RL. Dietary and serum folate: their influence on the outcome of pregnancy. Am J Clin Nutr 1996;63:520–5.
17. Scholl TO, Hediger ML, Schall JI, Fischer RL, Khoo CS. Low zinc intake during pregnancy: its association with preterm and very preterm delivery. Am J Epidemiol 1993;137:1115–24.
18. Scholl TO, Hediger ML. Anemia and iron-deficiency anemia: compilation of data on pregnancy outcome. Am J Clin Nutr 1994;59(suppl):492S–501S.
19. Scholl TO, Hediger ML, Bendich A, Schall JI, Smith WK, Krueger PM. Use of multivitamin-mineral prenatal supplement: influence on the outcome of pregnancy. Am J Epidemiol 1997;146:134–41.
20. Cikot RJLM, Steegers-Theunissen RPM, Thomas CMG, de Boo TM, Merkus HMWM, Steegers EAP. Longitudinal vitamin and homocysteine levels in normal pregnancy. Br J Nutr 2001;85:49–58.
21. Wang Y, Walsh SW, Guo J, Zhang J. The imbalance between thromboxane and prostacyclin in preeclampsia is associated with an imbalance between lipid peroxides and vitamin E in maternal blood. Am J Obstet Gynecol 1991;165:1695–700.
22. von Mandach U, Huch R, Huch A. Maternal and cord serum vitamin E levels in normal and abnormal pregnancy. Int J Vitam Nutr Res 1993;63:26–32.
23. Dreyfuss ML, Msamanga GI, Spiegelman D, et al. Determinants of low birth weight among HIV-infected pregnant women in Tanzania. Am J Clin Nutr 2001;74:814–26.
24. Lee BE, Hong YC, Lee KH, et al. Influence of maternal serum levels of vitamins C and E during the second trimester on birth weight and length. Eur J Clin Nutr 2004;58:1365–71.
25. Valsecchi L, Cairone R, Castiglioni MT, Almirante GM, Ferrari A. Serum levels of alpha-tocopherol in hypertensive pregnancies. Hypertens Pregnancy 1999;18:189–95.
26. Jagadeesan V, Prema K. Plasma tocopherol and lipid levels in mother and umbilical cord; influence on birth weight. Br J Obstet Gynaecol 1980;87:908–10.
27. Rumbold A, Crowther CA. Vitamin E supplementation in pregnancy. Cochrane Database Syst Rev 2005;2:CD004069.
28. Ben-Haroush A, Harell D, Hod M, et al. Plasma levels of vitamin E in pregnant women prior to the development of preeclampsia and other hypertensive complications. Gynecol Obstet Invest 2002;54:26–30.
29. Tamura T, Goldenberg RL, Johnston KE, Cliver SP, Hoffman HJ. Serum concentrations of zinc, folate, vitamins A and E, and proteins, and their relationships to pregnancy outcome. Acta Obstet Gynecol Scand 1997;76:63–70.

30. Boskovic R, Gargaun L, Oren D, Djulus J, Koren G. Pregnancy outcome following high doses of vitamin E supplementation. Reprod Toxicol 2005;20:85–8.
31. Ford ES, Sowell A. Serum α-tocopherol status in the United States population: findings from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 1999;150:290–300.
32. CDC. Infant health among Puerto Ricans–Puerto Rico and U.S. mainland, 1989–2000. MMWR Morb Mortal Wkly Rep 2003;52:1012–6.
33. Devaaraj S, Traber MG. γ-Tocopherol, the new vitamin E? Am J Clin Nutr 2003;77:530–1.
34. Jiang Q, Christen S, Shigenaga MK, Ames BN. γ-Tocopherol, the major form of vitamin E in the US diet, deserves more attention. Am J Clin Nutr 2001;74:714–22.
35. Leonard SW, Paterson E, Atkinson JK, Ramakrishnan R, Cross CE, Traber MG. Studies in humans using deuterium-labeled- α- and γ-tocopherols demonstrate faster plasma γ-tocopherol disappearance and greater γ-metabolite production. Free Radical Biol Med 2005;38:857–66.
36. Handelman GJ, Machlin LJ, Fitch K, Weiter JJ, Dratz EA. Oral α tocopherol supplements decrease plasma γ tocopherol levels in humans. J Nutr 1985;807–13.
37. Walsh SW. Eicosanoids in preeclampsia. Prostaglandins Leukot Essent Fatty Acids 2004;70:223–32.
38. Klockenbusch W, Goecke TW, Krüssel JS, Tutschek BA, Crombach G, Schrör K. Prostacyclin deficiency and reduced fetoplacental blood flow in pregnancy-induced hypertension and preeclampsia. Gynecol Obstet Invest 2000;50:103–7.
39. deJong CLD, Paarlberg KM, van Geijn HP, van Kamp GJ, van Dis H, Dekker GA. Maternal thromboxane and prostacyclin levels in relation to fetal birth weight. Eur J Obstet Gynecol Reprod Biol 2000;93:65–9.
40. Poston L, Briley AL, Seed PT, Kelly FJ, Shennan AH. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. Lancet 2006;367:1145–54.