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Original article

Vitamin E status and associations in maternal-infant Dyads in the Midwestern United States

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SUMMARY

Background: Oxidative stress has been associated with adverse neonatal outcomes, and vitamin E has powerful anti-oxidant properties. Vitamin E occurs in several different isoforms which differ in their ability to modulate inflammation and oxidative stress. Therefore, the purpose of this study was to evaluate the status of α-, γ- and δ-tocopherol in maternal-infant pairs, and the impact on maternal-newborn outcomes.

Methods: Vitamin E status was evaluated in 189 mother-infant pairs. Concentrations of α-, γ- and δ-tocopherol were measured using HPLC. Descriptive statistics were calculated and Spearman coefficients were used to assess correlations between maternal and cord measurements. Linear and logistic regression models were used to adjust for relevant confounders. A $p < 0.05$ was considered statistically significant.

Results: Maternal and cord serum tocopherol concentrations were positively correlated for γ-tocopherol ($r = 0.32$, $p < 0.001$) and δ-tocopherol ($r = 0.46$, $p < 0.001$) but not for α-tocopherol. After adjustment for confounders, maternal concentrations of tocopherols were positively associated with Apgar scores ($p = 0.02$) and infant growth parameters at birth. Conversely, cord tocopherol levels were inversely associated with Apgar scores ($p = 0.02$) and infant growth. Cord concentrations of α-tocopherol were higher in infants born to mothers with a diagnosis of pre-eclampsia ($p = 0.04$).

Conclusion: Maternal-fetal transfer of γ- and δ-tocopherols is higher than α-tocopherol and may be mediated by either different or more efficient methods, conversely tissue uptake of α-tocopherol by the developing fetus may be higher. As serum levels of maternal tocopherols are positively associated with outcomes while higher cord levels show a negative impact, uptake and tissue deposition of vitamin E by the fetus may be crucial in growth and development. More research into the role of maternal diet, placental regulation, and fetal uptake of vitamin E tocopherols in relation to clinical outcomes is warranted.

1. Introduction

Recent evidence supports the concept that during pregnancy, oxidative stress may be associated with low birth weight, preterm delivery, and pre-eclampsia [1–3]. Vitamin E is a powerful chain-breaking antioxidant and the primary lipid peroxyl radical scavenger in the human body [4]. It is of critical importance in early

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infancy, and deficiency in this population has devastating consequences such as intraventricular hemorrhage, bronchopulmonary dysplasia and delays in the development of the central nervous system [5].

Vitamin E occurs in nature in 8 different structurally related forms, including 4 tocopherol forms (α, β, γ, and δ) and 4 tocotrienols (α, β, γ, and δ) [6]. Alpha-tocopherol is quantitatively the major form in humans and has been extensively studied. In contrast, γ-tocopherol, which is the major form of vitamin E in the US diet, has received much less attention [6]. Additionally, very little is known about the β or δ isoforms. Recent evidence suggests that qualities that distinguish the isoforms are likely a result of unique metabolism and biological properties and they may have unique roles in human health and disease [7]. In contrast to the anti-inflammatory properties of the α-tocopherol isoform, the γ-tocopherol isoform has been shown to increase cytokine production (i.e.IL-2) and demonstrate pro-inflammatory properties [8–12]. Importantly, serum γ-tocopherol isoforms at as little as 10% of the concentration of α-tocopherol have been shown to ablate the anti-inflammatory benefit of alpha-tocopherol [11].

While the influence of tocopherols, primarily α-tocopherol, on fetal growth and other clinical outcomes has been examined [13]; the effects of γ-tocopherol are much less reported, and to our knowledge no study has reported the impact of δ-tocopherol. Recent evidence has demonstrated a relative abundance of the non-α-tocopherol isoforms, particularly γ- and δ-tocopherol, in various vegetable oils [14]. Since the consumption of these oils is high in North America, research into the impacts these compounds may have on conditions affected by inflammation and oxidative stress is warranted. We therefore investigated the relation of the most plentiful isomers of vitamin E, including α-, γ- and δ-tocopherols, with infant growth parameters at birth and other maternal-infant outcomes in a cohort of mother-infant pairs.

2. Materials and methods

This was a cross-sectional study evaluating vitamin E status of 189 maternal-infant pairs recruited from the Labor and Delivery unit, Newborn Nursery, and the Newborn Intensive Care unit in a Midwestern United States academic medical center. After obtaining IRB approval, samples of both cord and maternal blood were collected at the time of delivery from those who consented to participate. Exclusion criteria included congenital abnormalities, GI, liver, or kidney disease, or inborn errors of metabolism in the infant or the mother. Samples were protected from heat and light and processed and frozen at −80° within a maximum of 12 h.

2.1. Evaluation of serum concentrations

Analysis of samples was performed at the Biomarker Research Institute at the Harvard School of Public Health. Measurements of α-tocopherol, γ-tocopherol, and δ-tocopherol were obtained. Concentrations in plasma samples were measured as described by El-Sohemy et al. [15]. Plasma samples (250 μL) were mixed with 250 mL ethanol containing 10 ug *rac*-tocopherol/mL (Tocol) as an internal standard, extracted with 4 mL hexane, evaporated to dryness under nitrogen, and reconstituted in 100 mL ethanol-dioxane (1:1, by vol) and 150 mL acetonitrile. Samples are quantitated by high-performance liquid chromatography (HPLC) on a Restek Ultra C_{18} 150 mm × 4.6 mm column with a 3-μm particle size encased in a column oven (Hitachi L-2350, Hitachi, San Jose, CA) to prevent temperature fluctuations, and equipped with a trident guard cartridge system (Restek, Corp. Bellefonte, PA). A mixture of acetonitrile, tetrahydrofuran, methanol, and a 1% ammonium acetate solution (68:22:7:3) was used as the mobile phase at a flow rate of 1.1 mL/min, with a Hitachi L-2130 pump in isocratic mode, a Hitachi L-2455 diode array detector (300 nm and 445 nm), and a Hitachi L-2200 auto-sampler with water-chilled tray. Internal quality control was monitored with four control samples analyzed within each run and external quality control was monitored by participation in the standardization program for carotenoid analysis from the National Institute of Standards and Technology U.S.A. Reference values for tocopherol levels (mean ± SD) established from a large study of 1500 healthy American volunteers are 16,174.6 ± 5177.2 μg/L for α-tocopherol; 1538.6 ± 765.6 μg/L for γ-tocopherol, and 247.7 ± 116.9 μg/L for δ-tocophorol.

2.2. Evaluation of nutrient intake

The Willett Food Frequency Questionnaire (FFQ) was administered to all maternal participants at the time of delivery. A FFQ has distinct advantages over other methods for assessment of nutrient intake, such as 24 h recalls, as they are reflective of intake over time and can be used to assess intake during the course of the pregnancy. Additionally, many days of recall are required to estimate an individual's dietary intake of vitamin E accurately [16,17], making FFQ methodology the preferred method for our objectives. The Willet FFQ has been validated in adults of all ages and sexes, including pregnant women [18]. From responses to the questionnaire, individualized nutrient intake can be calculated based on the known nutrient content of foods. The FFQ was analyzed by trained personnel at the Harvard School of Public Health.

2.3. Other study variables

Demographic information collected on all maternal participants included age, race, ethnicity, marital status, and pre-pregnancy Body Mass Index (BMI). Smoking was self-reported by the mother at the time of admission. Clinical maternal outcomes evaluated included: 1) mode of delivery, defined as vaginal vs. Cesarean-section; 2. A diagnosis of chorioamnionitis; and 3) a clinical diagnosis of pre-eclampsia.

Infant clinical data collected at the time of delivery included gestational age, race, birth weight, length, Apgar scores, and head circumference. Infants were weighed by nursing staff daily on a gram scale, and head circumference and length in centimeters were recorded weekly. Fenton growth curve percentile rankings were calculated and plotted electronically for each recorded anthropometric measurement.

2.4. Statistical analysis

Means, standard deviations, counts and percentages were used to summarize the data. Spearman correlations coefficients were used to look at the association of maternal and cord measurements. Independent sample t-tests were used to compare continuous measures between dichotomous groups. Linear and logistic regression models were used to adjust associations significant in the univariate analysis for the potential confounders. Potential confounding variables of gestational age and smoking were chosen based on associations with infant birth weight and fetal growth and also with serum tocopherol measurements were included in the multivariate models. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

The final number of participants in our study was 189 mothers and infants. Of those, 180 mothers and 173 infants had blood samples available at the time of delivery. Eighteen percent of infants were premature, defined as ≤37 weeks gestational age at birth. The estimated mean vitamin E intake (as α-tocopherol) in the maternal cohort was 20.5 mg, above the Recommended Dietary Intake for pregnant women (15 mg), however 43% of women had vitamin E intakes below the Estimated Average Requirement (EAR) of 12 mg/day. Of note, white mothers had significantly higher serum levels of α-tocopherol compared to non-white mothers (13.381.3 vs. 11,048.6 for whites vs. non-whites, respectively, $p = 0.0007$). Baseline characteristics of the maternal and infant cohort are given in Table 1.

Cord concentrations of γ-tocopherol were positively correlated with maternal pre-pregnancy BMI ($r = 0.29$, $p = 0.003$). Cord levels of γ-tocopherol were also inversely associated with gestational age at birth ($r = -0.17$. $p = 0.03$), however no other serum tocopherol levels were significantly associated with gestational age.

Table 1
Characteristics of the maternal and infant cohort.

Maternal/infant Characteristic continuous variables:	N	Mean (SD)
Maternal age (years)	189	28.7 (5.6)
Maternal BMI (kg/m^2)	112	27.1 (6.6)
Infant corrected gestational age at birth (weeks)	189	38.04 (3.1)
Infant birth anthropometrics:		
Birth weight (g)	189	3109.8 (783.4)
Birth length (cm)	189	48.4 (4.7)
Birth head circumference (cm)	189	33.5 (2.8)
Maternal serum levels (μg/L)		
α-tocopherol	180	12,512.2 (4672.8)
γ-tocopherol	180	1458.3 (729.4)
δ-tocopherol	180	304.9 (173.5)
Infant serum (cord) levels (μg/L)		
α-tocopherol	173	1948.1 (804.5)
γ-tocopherol	173	246.1 (200.1)
δ-tocopherol	173	107.8 (74.5)
Maternal dietary vitamin E intake (mg/day)		
α-tocopherol	132	20.5 (30.1)
γ-tocopherol	132	9.7 (4.5)
δ-tocopherol	132	2.2 (1.2)
Categorical variables:	**N**	**%**
Maternal race		
White	111	58.7
African-American	28	14.8
Hispanic	24	12.7
Asian/Pacific islander	3	1.59
Other	23	12.7
Smoking status		
Current smokers	28	15
Former/never smokers	148	85
Mode of delivery		
Cesarean section	63	35
Vaginal delivery	114	65
Maternal diagnosis of pre-eclampsia		
No	174	92
Yes	15	8
Maternal diagnosis of chorioamnionitis		
No	169	64
Yes	10	6
Infant gender		
Male	96	51
Female	93	49

3.2. Maternal-cord transfer of vitamin E tocopherols

Maternal and cord serum tocopherol concentrations were positively correlated for γ-tocopherol ($r = 0.32$, $p < 0.001$) and δ-tocopherol ($r = 0.50$, $p < 0.001$). In contrast, maternal α-tocopherol concentrations were not associated with cord concentrations ($p = 0.56$).

3.3. Maternal dietary intake correlations

Maternal intake of α-tocopherol was inversely associated with maternal serum concentrations of both γ-tocopherol and δ-tocopherol ($r = -0.20$, $p = 0.02$; and $r = -0.27$, $p = 0.002$ for γ- and δ-tocopherols, respectively), while maternal intake of α-tocopherol demonstrated a trend towards a positive association with cord α-tocopherol concentrations ($r = 0.17$, $p = 0.06$).

3.4. Tocopherol associations with clinical outcomes

Maternal concentrations of α-tocopherol showed positive associations with infant weight percentile ranking, length and length percentile ranking, and head circumference and head circumference percentile ranking at birth in the univariate analysis. After adjustment for gestational age and smoking status, higher maternal concentration of α-tocopherol retained a significant association with improved growth parameters in the newborn. Similarly, after adjustment for these same confounders, γ-tocopherol concentrations showed positive associations with birth weight, weight percentile ranking, and head circumference, and δ-tocopherol showed positive associations with birth weight and birth weight percentile ranking. These relationships are shown in Table 2.

In contrast to positive associations between maternal serum tocopherol concentrations and growth outcomes, α-tocopherol concentrations in cord blood showed inverse associations with birth weight and birth weight percentile ranking, as did γ-tocopherol. These relationships are shown in Table 3.

Serum concentrations of both α- and γ-tocopherol were significantly higher in the cord blood of babies born with low birth weight (LBW, ≤2500 g) (2419.0 vs 1882.7 μ/L, $p = 0.01$ for α-tocopherol; and 343.5 vs. 213.5 μ/L, $p = 0.001$ for γ-tocopherol for infants with LBW vs. those without). These associations remained significant after adjustment for gestational age and smoking ($p = 0.005$ and 0.002 for α- and γ-tocopherol, respectively).

In the univariate analysis, both maternal and cord blood serum levels of α-tocopherol were associated with 5-min Apgar scores ($r = 0.17$, $p = 0.03$; $r = 0.16$, $p = 0.03$ for maternal and cord blood levels, respectively). After adjustment for confounders, maternal α-tocopherol levels maintained a positive association with Apgar scores ($\beta = 0.00004$, $p = 0.02$), while cord levels of α-tocopherol demonstrated an inverse relationship with Apgar scores ($\beta = -0.0003$, $p = 0.02$).

Cord blood levels of α- and γ-tocopherol levels were associated with a diagnosis of preeclampsia, with infants born to mothers with preeclampsia having higher concentrations of α-tocopherol (2543.8 vs. 1943.4 μg/L) for with vs. without preeclampsia, respectively, $p = 0.005$) and higher levels of γ-tocopherol (288.7 vs 233.0 μg/L for with vs. without preeclampsia, respectively, $p = 0.006$). After adjustment for smoking status, cord concentrations of α-tocopherol retained a significant association with a maternal diagnosis of preeclampsia ($p = 0.04$), while the association between γ-tocopherol and a diagnosis of preeclampsia was attenuated ($p = 0.15$). Maternal concentrations of γ-tocopherol were also higher in mothers who delivered via cesarean compared to vaginal delivery (1595.8 vs. 1353.1 μg/L, respectively, $p = 0.003$). After adjustment for smoking status and gestational age, this relationship remained

Table 2
Maternal vitamin E isoform concentration and newborn weight, length, head circumference and percentile rakings at birth.

	Weight[a]		Weight %ile[b]		Length[a]		Length %ile[b]		Head circumference[a]		Head circumference %ile[b]	
Vitamin E isoform (μg/L)	β	p	β	p	β	p	β	p	β	p	β	p
α	–	–	0.0001	0.04	0.0001	0.03	0.0005	0.03	0.00007	0.03	0.001	0.03
γ	0.10	0.04	–	–	–	–	–	–	–	–	–	–
δ	0.47	0.02	0.02	0.05	–	–	–	–	–	–	–	–

[a] Models adjusted for gestational age and smoking.
[b] Models adjusted for smoking (percentile rankings are gestational age adjusted measures).

Table 3
Infant (Cord) vitamin E isoform concentration and newborn weight, length, head circumference and percentile rakings at birth.

	Weight[a]		Weight %ile[b]		Length[a]		Length %ile[b]		Head circumference[a]		Head circumference %ile[b]	
Vitamin E isoform (μg/L)	β	p	β	p	β	p	β	p	β	p	β	p
α	−0.15	0.0001	−0.009	0.002	–	–	−0.008	0.01	–	–	–	–
γ	−0.41	0.04	−0.03	0.05	–	–	–	–	–	–	–	–
δ	–	–	–	–	–	–	–	–	–	–	–	–

[a] Models adjusted for gestational age and smoking.
[b] Models adjusted for smoking (percentile rankings are gestational age adjusted measures).

significant ($p = 0.04$ in adjusted models). Maternal levels of α-tocopherol were 12,614.6 μg/L in mothers without chorioamnionitis compared to 10,047.9 μg/L in those with ($p = 0.057$). Similar results were seen for γ-tocopherol (1467.6 μg/L vs. 1070.7 for no vs. yes diagnosis of chorioamnionitis, $p = 0.05$).

4. Discussion

This study expands the previous findings related to the maternal-fetal transfer of vitamin E tocopherols and shows that while maternal serum levels of α-tocopherol were not correlated with the infant's levels at birth, maternal levels of γ- and δ-tocopherol did have a significant relationship with cord levels. Additionally, while higher maternal levels of vitamin E tocopherols were associated with improved infant growth parameters and Apgar scores at birth, higher cord concentrations of tocopherols were inversely associated with these parameters.

While the transfer of α-tocopherol from the mother to the fetus has been studied, this relationship in other vitamin E compounds is not well understood. Our study reports significant correlations between serum levels of γ-tocopherol in mothers and their infants, and to our knowledge is the first to report this association for δ-tocopherol. This association was not seen for α-tocopherol, which is in agreement with other reports [19–21]. A recent cross-sectional study by da Silva Ribeiro et al. evaluated whether maternal α-tocopherol concentration levels were associated with α-tocopherol levels of the newborn and found the α-tocopherol level in umbilical cord was 20% of that in maternal serum [22]. Keily et al. evaluated plasma levels of α- and γ-tocopherol concentrations in 40 mother infant pairs and found results similar to ours, with a correlation between γ-tocopherols concentrations in the mothers and infants ($r = 0.45$, $p = 0.0005$), but no association between concentrations of α-tocopherol [19]. We expand on these findings and report that serum concentrations of δ-tocopherol are also correlated in mother-infant pairs; indeed, this was the strongest correlation present in our study. Unlike other fat soluble vitamins, vitamin E does not have a specific carrier protein in the serum for transport. It circulates in each tocopherol form in serum lipoproteins, together with other lipids [23]. A cellular binding protein exists in the liver, and it has been suggested that this protein, called α-tocopherol transfer protein (α-TTP) enables the transfer of α-tocopherol between membranes and its incorporation into lipoproteins. It appears that only α-tocopherol is able to bind this protein with high affinity [23]. It is possible that immaturity in this protein system in the infant leads to low levels of α-tocopherol in lipid components, and hence in cord plasma. It has been speculated that the lower transport capacity in newborns may be a reflection of the low cord levels of LDL and of lipids [21]; however, the cord plasma concentration of γ-tocopherol (which was less than one-fifth that of maternal plasma level) showed a high correlation with maternal plasma γ-tocopherol level, similar to findings by Yeum et al., in 1998 [21]. It is also possible that the low α-tocopherol serum levels seen at birth are reflective of increased tissue uptake and deposition in the newborn infant. Importantly, evidence from animal models demonstrates that although α-tocopherol concentrations are low or even undetectable in newborn lambs, brain and *semimembranosus* muscle concentrations were increased significantly in lambs born to α-tocopherol supplemented ewes [24].

We also report that maternal serum tocopherol levels were positively associated with Apgar scores and newborn growth parameters at birth. Prior studies of vitamin E status and newborn growth outcomes have focused primarily on the α-tocopherol isoform. Two studies have reported that third-trimester α-tocopherol concentrations are lower in small for gestational age (SGA) cases when compared to controls [13,25]. Turner et al. reported a positive association between maternal plasma α-tocopherol and crown-rump length in the first trimester. Crown-rump length was associated with measurements of lung function at 5 years of age, suggesting that maternal vitamin E status might be a determinant of fetal growth and lung development [26].

In one of the only studies to examine the γ-tocopherol isoform in relation to clinical outcomes, Scholl et al. reported that plasma concentrations of α-tocopherol at entry to care and at week 28 of pregnancy in 1231 United States women were positively related to increased fetal growth (birth weight for gestational age), a decreased risk of small for gestational age births, and an increased risk of large for gestational age births, however no relationships were seen between fetal growth outcomes and γ-tocopherol [13]. We now provide additional data reporting that maternal concentrations of δ- and γ-tocopherol were also positively associated with infant birth weight.

We also report a positive association between 5-min Apgar scores at delivery and maternal levels of α-tocopherol. Very few other studies have evaluated vitamin E status in relation to Apgar scores at delivery. In one such study to do so, 104 pregnant women were randomized to receive 400 IU of vitamin E or placebo from 14 weeks of gestation until delivery. Although not statistically significant, there was a trend towards higher mean 5-min Apgar scores in

the vitamin E supplemented group ($p = 0.09$) [27]. Biochemical assessments of vitamin E status were not performed as part of this study.

An interesting finding in our study is the inverse association between cord levels of tocopherols and both Apgar scores and growth parameters, including birth weight and the incidence of LBW, which is in direct contrast to the positive associations seen with maternal serum levels. While serum maternal tocopherols may have a direct impact on fetal growth, it is plausible that higher levels of vitamin E tocopherols in cord blood represent a decreased tissue uptake of tocopherols by the fetus, resulting in poorer Apgar scores and growth outcomes relative to infants with a higher tissue deposition of tocopherols. It is also possible these outcomes could be related to pro-inflammatory activity ascribed to increased levels of γ-tocopherol, or that the anti-inflammatory activities of α-tocopherol were reduced by the high levels of γ-tocopherol in cord blood. Conversely, it could also be hypothesized that higher cord tocopherol concentrations are a consequence of placental dysfunction, and the increase cord tocopherol concentrations are a biomarker of that process. Evaluation of both levels and the metabolites of α- and γ-tocopherol in cord blood may provide further clarity surrounding this question in future investigations.

Similarly, our study reports that infants born to women with pre-eclampsia had higher levels of α-tocopherol in cord blood samples compared to infants born to non-pre-eclamptic mothers. The pathophysiology of pre-eclampsia and growth restriction are not entirely understood, but endothelial dysfunction may play a role in both conditions. Oxidative stress, caused by increased production of free radicals and insufficient antioxidant defenses, is a known cause of endothelial dysfunction [28], and thus may be related to both pre-eclampsia and newborn growth restriction. In one study designed to evaluate the impact of vitamin C and E supplementation in high-risk women to prevent preeclampsia, supplementation reduced the risk of preeclampsia but did not increase fetal growth [1]. In contrast to these findings, a 2006 multicenter trial of 2410 pregnant women at risk for pre-eclampsia 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 a low birth weight infant (˂2500 g) [29]. With regard to specific tocopherol isoforms, a systematic review conducted by Cohen et al. reported that several studies have suggested that higher levels of γ-tocopherol may be associated with a modest increase in the risk of pre-eclampsia, however the authors noted that small, low-quality studies limit the conclusions that can be drawn [28]. In our study, the inverse associations between cord blood tocopherols and growth, combined with the higher levels of cord blood tocopherols in infants of pre-eclamptic mothers, may suggest that placental dysfunction results in higher levels of tocopherol isoforms in the newborn infant.

The mean vitamin E intake (as α-tocopherol) in our maternal cohort was 20.5 mg, and 43% of women had intakes that were below the Estimated Average Requirement (EAR) of 12 mg/day. In contract to this, NHANES data from 2001 to 2002 has shown that women of childbearing age in the U.S. (14–50 years), more than 97% of women do not meet the EAR [30]. It is possible the use of prenatal vitamins, which typically contain α-tocopherol, was a factor in increasing the vitamin E intake of our cohort. Additionally, our study finds that women with a higher BMI had higher serum levels of the γ-tocopherol isoform. This is consistent with findings in post-menopausal women [31], however this relationship remains poorly understood. It is possible the higher γ-tocopherol levels in obese women are reflective of lower quality dietary patterns in this population. Similarly, our findings of higher γ-tocopherol levels in mothers who delivered via C-section may be related to increased BMI, as we found a positive relationship between maternal γ-tocopherol levels and BMI, a known predictor of C-section [32,33].

Our study has several limitations. Our sample size is small, and did not allow for the adjustment of the many confounders that may likely have an impact on infant growth. For this reason, we did not include serum cholesterol levels or other measurements of lipid status in our models. The lipid status of our maternal cohort was normal (range of serum cholesterol levels: 104–181 mg/dL) and other studies have shown that in pregnant women, both cholesterol-adjusted and unadjusted models give similar results [13,21]. Gestational age and smoking were selected for inclusion in our models as these factors are likely to have a large impact on infant outcomes.

5. Conclusion

Maternal-fetal transfer of γ- and δ-tocopherols is higher than α-tocopherol and may be mediated by either different or more efficient methods, conversely tissue uptake of α-tocopherol by the developing fetus may be higher. As serum levels of maternal tocopherols are positively associated with outcomes while higher cord levels show a negative impact, uptake and tissue deposition of vitamin E by the fetus may be crucial in growth and development. More research into the role of maternal diet, placental regulation, and fetal uptake of vitamin E tocopherols in relation to clinical outcomes is warranted.

Author contribution

CH, EL, JF, MVO, MS, AK, EM, KR, EE, CC, RJ, KW and AAB conceived and designed the experiments, performed the experiments, analyzed the data, and wrote the paper.

Conflicts of interest

CH, EL, JF, MVO, MS, AK, EM, EE, KR, CC, RJ, KW and AAB declare no conflicts of interest.

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