

Absorption, Transport, and Bioavailability of Vitamin E and its Role in Pregnant Women

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Abstract

Vitamin E is an important lipophilic antioxidant. The term refers to eight essential naturally occurring fat-soluble nutrients called tocopherols or tocotrienols. Among these isomers, α -tocopherol has the highest biologically active form and is found in all lipoprotein fractions. Vitamin E deficiency during pregnancy may cause miscarriage, preterm birth, preeclampsia, and intrauterine growth restriction. This review highlights recent findings that have led to a better understanding of vitamin E absorption, transport, bioavailability, and its role in pregnancy, and that underline the need for re-evaluation of the potential benefits of vitamin E supplementation in pregnant women.

Résumé

La vitamine E est un important antioxydant lipophile. Ce terme fait référence aux huit nutriments liposolubles essentiels d'origine naturelle connus sous le nom de tocophérols ou de tocotriénols. Parmi ces isomères, l' α -tocophérol constitue la forme active sur le plan biologique la plus élevée et fait partie de toutes les fractions lipoprotéiniques. La carence en vitamine E au cours de la grossesse peut entraîner une fausse couche, un accouchement préterme, une prééclampsie et un retard de croissance intra-utérin. La présente analyse met en évidence les données récentes qui ont mené à une meilleure compréhension de l'absorption, du transport et de la biodisponibilité de la vitamine E (et de son rôle pendant la grossesse), et qui soulignent la nécessité de réévaluer les avantages potentiels de la supplémentation en vitamine E chez les femmes enceintes.

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INTRODUCTION

“Vitamin E” refers to a family of tocopherol and tocotrienol isomers discovered in 1922 as anti-infertility factors.¹ Because of its important role in fertility,² vitamin E has been named tocopherol from the Greek words *tokos*, meaning childbirth, and *phero*, meaning to bring forth, whereas the *ol* ending indicates the alcohol property of this

molecule.³ There are eight forms of this lipophilic antioxidant: α -, β -, γ -, and δ -tocopherol and α -, β -, γ -, and δ -tocotrienol (Figure 1).⁴ Tocopherols have a completely saturated chain, whereas tocotrienols are characterized by three trans double bonds (partially unsaturated chain).⁵ Tocotrienols are believed to have powerful neuroprotective, anticancer, and cholesterol-lowering properties, although there is little published evidence concerning their effectiveness.⁶ With respect to tocopherols, although γ -tocopherol is the major form of dietary vitamin E, α -tocopherol is the most important form of vitamin E present in human plasma and tissues.⁷ The synthetic α -tocopherol (all racemic α -tocopherol) consists of an equal racemic mixture of the eight stereoisomers (*RRR*, *R₂S*, *RRS*, *R₃S*, *SRR*, *S₂S*, *SRS*, and *SSS*), whereas the natural form of α -tocopherol is found only in the *RRR* configuration.⁸ Vitamin E, as well as other lipophilic components such as fatty acids, cholesterol, and other liposoluble vitamins, is absorbed in the small intestine. While in enterocytes, vitamin E is incorporated into chylomicrons, which pass into the lymphatic system and the circulation. The capacity to increase α -tocopherol concentrations in plasma is limited because α -tocopherol is replaced by newly absorbed α -tocopherol,⁹ whereas the surplus is excreted in bile.

ORIGIN AND METABOLISM OF VITAMIN E

Dietary Sources of Vitamin E

Depending on the major sources of vegetable oils, dietary intake of β - and δ -tocopherol can be minimal. Dietary intake in γ -tocopherol normally exceeds that of α -tocopherol. Indeed, in the United States it has been estimated that approximately 70% of the vitamin E intake from food is in the γ -tocopherol form, probably due to the high intake of soybean, containing 8 mg/100 g of α -tocopherol and 70 mg/100 g of the γ -form, or corn oil, containing 20 mg/100 g of α -tocopherol and 70 mg/100 g of the

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γ -form.¹⁰ Even though dietary intakes of γ -tocopherol are 10-fold higher than α -tocopherol, the latter represents the major form of vitamin E in plasma. In fact, the percentage of plasma γ -tocopherol represents only 10% to 20% of total vitamin E.¹¹

Inconsistency in the assessment of vitamin E contents of prepared foods should be considered when interpreting results from a number of dietary intervention studies. This variability can be explained by many factors, such as genetics, season, harvesting conditions, climate, ripeness, freshness, food matrix, and food processing.^{12–15} In some vegetables, such as broccoli, cauliflower, Brussels sprouts, and cabbage, variations in content from 0 to 83% for α -tocopherol and 0 to 100% for γ -tocopherol have been reported.¹⁶ Thus, concentrations of vitamin E ranging from 122 mg/kg to 612 mg/kg in ripe tomato fruit have been reported.¹⁷ In addition, conditions of storage (oxygen, ultraviolet light, and temperature) may affect the vitamin E content.¹⁸ In general, α -tocopherol decomposes faster than γ -tocopherol.¹⁹

Intestinal Absorption and Plasma Transport of Vitamin E

The digestion of vitamin E in the small intestinal lumen is similar to that of dietary fats (Figure 2). This lipid-soluble vitamin requires biliary and pancreatic secretions in order to form micelles for subsequent uptake by intestinal epithelial cells.²⁰ Vitamin E intestinal absorption is, in part, mediated by scavenger receptor class B type 1 (SR-B1), in a mechanism similar to that of cholesterol uptake.²¹ Intestinal absorption of vitamin E involves complex mechanisms such as intracellular trafficking proteins, the modulation of nuclear receptors, and the activity of adenosine triphosphate binding cassette transporters.²² Dispersion of vitamin E in the intestinal lumen, together with dietary lipids, can markedly influence vitamin E digestion and absorption.²³ These findings support the concept of varying

degrees of vitamin E bioavailability. Upon entering the circulation via the thoracic lymph, chylomicron triglycerides are hydrolyzed by endothelium-bound LPL, resulting in the production of chylomicron remnants. Released fatty acids and some vitamin E molecules are then transferred to peripheral tissues,²⁴ whereas chylomicron remnants, also carrying vitamin E, are then taken up by hepatic endocytosis through a receptor-mediated mechanism.²⁵

Hepatic Metabolism of Vitamin E

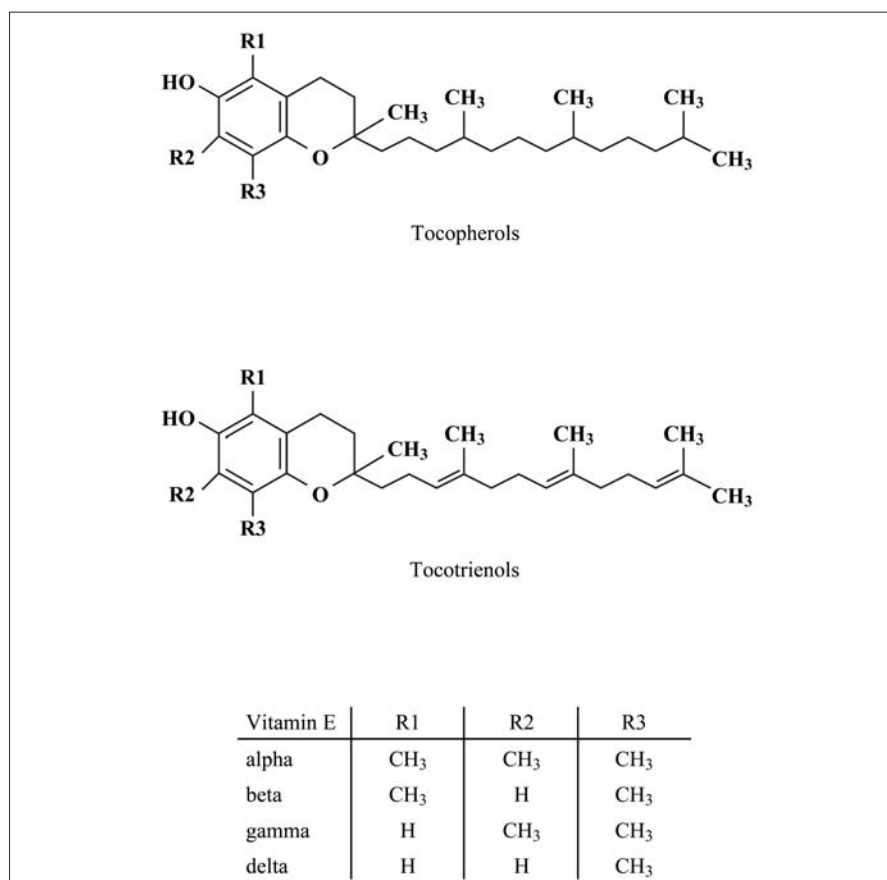
Hepatic receptors, e.g., the LDL-cholesterol receptor and the LDL receptor-related protein, are largely implicated in this uptake process.^{26,27} The hepatic α -tocopherol form of vitamin E is specifically selected by the α -TTP, a small cytoplasmic hepatic protein with differential affinity for α -tocopherol.^{27–29} This protein is expressed not only in the liver but also in human brain and placenta,³⁰ thus limiting the use of other forms of vitamin E in humans.²⁷ Other hepatic forms of vitamin E, i.e., β -, γ - and δ -, and the excess of α -tocopherol are then excreted into the bile^{31,32} or metabolized by side chain degradation via initial P450 enzymatic degradation (ω -oxidation) and subsequent β -oxidation^{33,34} to form carboxyethyl-hydroxychroman.³⁵ Finally, this main metabolite of tocopherols is largely excreted in urine. The α -CEHC, the metabolite of α -tocopherol, is excreted only in the urine of healthy subjects when a certain plasma α -tocopherol threshold is exceeded.³⁶ On the basis of these observations, it has been suggested that α -tocopherol might be degraded only after an optimum plasma level has been achieved.³⁷ As a consequence, α -CEHC excretion could be taken as a marker for optimal α -tocopherol supply.

The function of α -TTP is to incorporate vitamin E taken up by liver cells into VLDL-cholesterol,³⁸ but the exact mechanism is still not well understood. Similarly to chylomicron particles, VLDL triacylglycerols are catabolized by LPL at the surface of the vascular endothelium of peripheral tissues transferring α -tocopherol to adjacent tissues and HDL-cholesterol particles.³⁹ Approximately 50% to 60% of VLDL remnant particles (or IDL-cholesterol) thus formed are taken up by the liver, while the remaining 40% to 50% is catabolized into LDL and delivered to other peripheral tissues.³⁹ Finally, α -tocopherol exchanges also take place between LDL and HDL particles that are important for vitamin E transport in the circulation and delivery to reproductive tissues (e.g., adrenals, ovaries, and testes) and other tissues, specifically liver, lung and brain. The acquisition of α -tocopherol by these tissues appears to be mainly mediated via the SR-BI receptor.⁴⁰

ABBREVIATIONS

α -TTP	α -tocopherol transfer protein
CEHC	carboxyethyl-hydroxychroman
HDL	high density lipoprotein
IDL	intermediate density lipoprotein
LDL	low density lipoprotein
LPL	lipoprotein lipase
LRP	LDL receptor-related protein
P450	enzymatic degradation
TOH	tocopherol
Vit E	vitamin E
VLDL	very low density lipoprotein

Figure 1. Variations in the chemical structure of α -, β -, γ - and δ -vitamin E resulting from the number and arrangement of methyl groups surrounding the chromanol ring. Attached to this ring is a phytyl side chain (16 carbons) which is saturated in positions 3, 7, and 11 for tocopherols and unsaturated for tocotrienols.³⁹



Bioavailability

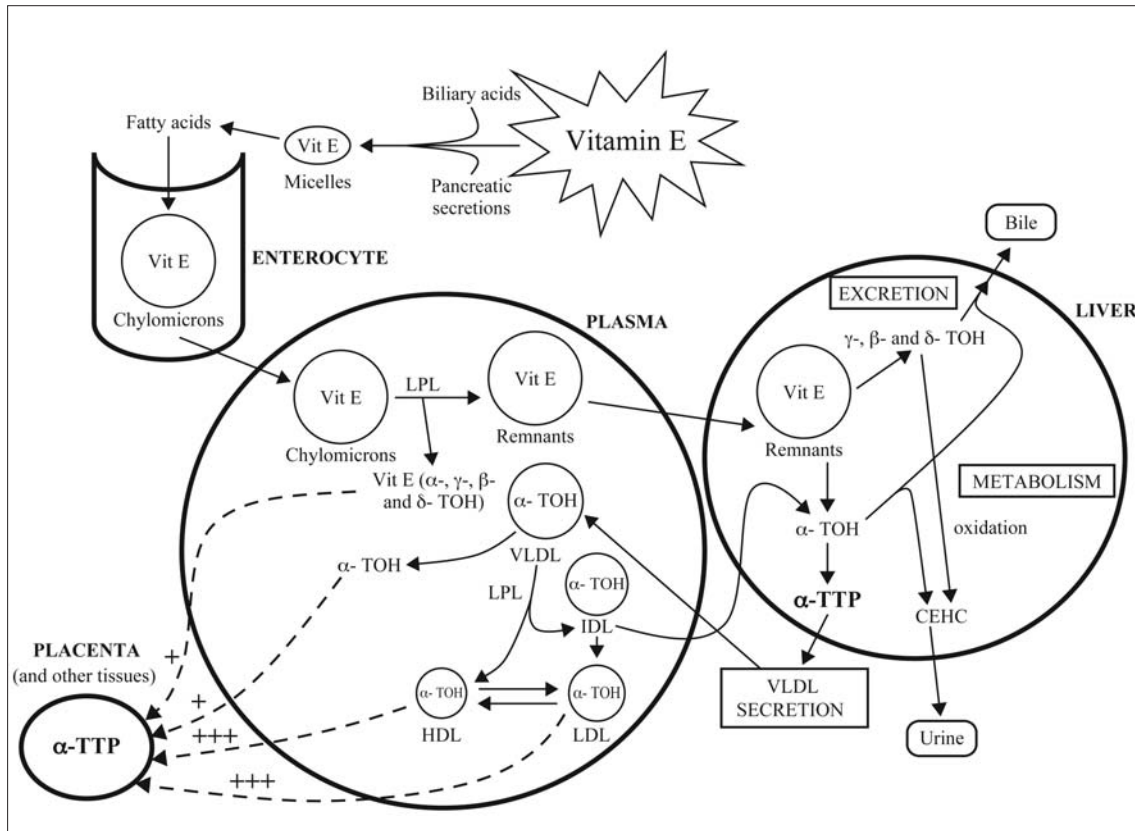
Bioavailability can be defined as the fraction of a food substance placed at the disposal of tissues after ingestion. The bioavailability of vitamin E in the human is regulated by many factors and is generally assessed using the level of plasma tocopherol. This availability is essential for biological activity since only this fraction has a physiological activity. Vitamin E bioavailability depends also on its dispersion in the intestinal lumen and the co-ingestion of other fat components, namely fatty acids and plant sterols.⁴¹ Indeed, vitamin E bioavailability is greatest when administered with food,⁴² indicating that the amount of fat and food matrix are important for vitamin E absorption²⁴ and that plasma lipid status influences uptake of α -tocopherol. A recent study revealed that vitamin C, carotenoids, and polyphenols significantly impaired the intestinal absorption of α -tocopherol.⁴³ The plasma concentrations of this micronutrient may be influenced by gene regulating intestinal uptake, intracellular trafficking, and lipoprotein secretion of vitamin E.⁴⁴ Reboul et al. suggest that SR-B1

expression and/or activity may explain the highly significant inter-individual variability found in tocopherol absorption.²¹ Some other studies have observed that maternal vitamin E levels increased significantly during pregnancy^{45,46} despite the marked increase in plasma volume during pregnancy, suggesting an increase in bioavailability during pregnancy.

Role of α -Tocopherol

For many years, α -tocopherol has primarily been well-known for its capacity to protect lipids and lipoproteins against peroxidative damage,^{39,47} but recently, it has been proposed that, under physiological conditions α -tocopherol may not act only as an antioxidant.⁴⁸ Thus, α -tocopherol would have other important biological functions, such as altering gene expression, modulating cell signalling and proliferation.³⁹ It also has significant effects on platelet adhesion,³ redox-regulated transcription, cytokine signalling, and perinatal immunoglobulin E production in atopic diseases.⁴⁹ In addition, α -tocopherol inhibits protein

Figure 2. Absorption, transport, secretion, and metabolism of vitamin E.



kinase C, 5-lipoxygenase and phospholipase A2, and activates protein phosphatase 2A and diacylglycerol kinase.³ Furthermore, decreases in α -tocopherol concentrations induce vulnerability in cell membrane from increased permeability.

The α -tocopherol isoform of vitamin E inhibits radical chain propagation within lipid domains by conversion into its oxidized product, α -tocopherylquinone. The balance between vitamin E and other antioxidants, such as ascorbate (vitamin C), may be crucial for antioxidant protection in vivo. α -Tocopherol can act either as an antioxidant or a pro-oxidant to inhibit or facilitate lipid peroxidation in LDL particles. However, this pro-oxidant activity of α -tocopherol is prevented by ascorbate acting as a co-antioxidant.⁵⁰ Indeed, the reduced form of vitamin E can be regenerated by a reduction in the activity of ascorbate,^{3,31,51} preventing oxidation of other lipoproteins by α -tocopherylquinone.⁵² Moreover, recent research has suggested that vitamin C has a dose-dependent effect on α -tocopherol in elderly patients with type 2 diabetes,⁵³ adding one more argument to support the hypothesis that vitamin C has the capacity to modulate α -tocopherol levels positively.

Role of γ -Tocopherol

γ -Tocopherol has a number of beneficial effects, including reducing in platelet aggregation, occlusive thrombus, arterial superoxide anion generation, lipid peroxidation and LDL oxidation, and increasing endogenous SOD activity.⁵⁴ γ -Tocopherol and its metabolite can also reduce synthesis of PGE₂, which plays a key role in inflammation.⁵⁵ In addition, γ -tocopherol is superior to α -tocopherol in controlling damage caused by reactive nitrogen oxide species^{56,57} and in reducing oxidative DNA damage.⁵⁸ Recent studies have indicated that γ -tocopherol could be inversely associated with the incidence of cardiovascular disease and prostate cancer.^{59,60} In addition, the 2,7,8-trimethyl-2-(2'-carboxyethyl)-6-hydroxychroman (γ -CEHC), the metabolite of γ -tocopherol, can inhibit cyclo-oxygenase activity, resulting in an anti-inflammatory effect.⁶¹

Interactions Between α - and γ -Tocopherol

After high-dose administration of α -tocopherol, several studies have observed a decrease in γ -tocopherol,⁶¹ which may be due to accelerated γ -tocopherol metabolism with the induction of a catabolic enzyme. Kiyose²⁸ reported urinary excretion of γ -CEHC in vitamin E-deficient rats after α - and γ -tocopherol supplementation, suggesting that

Published studies assessing the effects of vitamin E and vitamin C supplementation in the prevention of preeclampsia

Study	Recruitment (weeks of gestation)	Dosage/day	Vitamin E form	Plasmatic dosage (HPLC)	Observations
Chappell et al. ⁸⁴ (n = 283)	16–22	400 IU vit E + 1000 mg vit C	Natural-source vitamin E	Yes	Reduction in risk of preeclampsia
Beazley et al. ⁸⁵ (n = 100)	14–20	400 IU vit E + 1000 mg vit C	Not described	No	No effect
Rumbold et al. ⁸⁶ (n = 1877)	14–22	400 IU vit E + 1000 mg vit C	d- α -tocopherol succinate	No	No effect
Poston et al. ⁷⁰ (n = 2410)	14–21	400 IU vit E + 1000 mg vit C	RRR- α -tocopherol	Yes but not all	No reduction in PE risk, increase in low birthweight

α -tocopherol could influence the transformation of γ -tocopherol to γ -CEHC. Additionally, Eichhorn et al.⁶² showed that a decrease in γ -tocopherol did not increase the excretion of γ -CEHC, which may imply that other degradation and excretion routes are present for γ -tocopherol. During γ -tocopherol administration, levels of plasma α -CEHC significantly decreased and urinary excretion of α -CEHC tended to increase, probably due to acceleration in the metabolism of α -tocopherol.⁶¹

VITAMIN E SUPPLEMENTATION

Vitamin E oral supplementation results in variable increases in plasma α -tocopherol concentrations. Such variations may result from changes in regulatory factors such as α -TTP activity, metabolic rate, lipid content and composition, the status of other micronutrients recycling α -tocopherol, and environmental conditions.⁶³ As intestinal absorption is also highly variable, parenteral administration of vitamin E may represent an efficient alternative.³⁹ Vitamin E supplementation in amounts ≤ 1600 IU⁶⁴ has been reported to be safe for most adults in the prevention of oxidative stress.⁶⁵ However, two studies have suggested that administration of more than 400 IU/day of vitamin E may increase the risk of all-cause mortality⁶⁶ and heart failure.⁶⁷ Bjelakovic et al.⁶⁸ have reported that antioxidant supplements for primary and secondary prevention of several diseases, including atherosclerosis, may increase mortality. However, Chappell et al.⁶⁹ reported that antioxidant supplementation in women who were at risk of preeclampsia was associated with improvement in biochemical indices of the disease, an opinion that was later re-evaluated by the same authors.⁷⁰

VITAMIN E AND PREGNANCY

As an antioxidant molecule, vitamin E can decrease oxidative stress,^{69,71} but it is also an essential nutrient in the

normal physiology of reproduction. Indeed, female rats fed on a vitamin E-free diet are sterile, and impaired fertility has been observed in animals lacking α -TTP,³⁰ suggesting that vitamin E may play an important role in human reproduction. Furthermore, it has been suggested that α -TTP plays a major role in supplying the placenta and consequently the fetus with α -tocopherol in the pregnant mouse.⁷² The placenta has a higher discriminating capacity for vitamin E than the liver, as it preferentially selects natural rather than synthetic vitamin E. Several investigators^{73–75} have suggested that the α -TTP mediated transfer of vitamin E would be responsible for the preferential uptake of natural vitamin E in animals. Acuff et al.⁷⁶ also concluded that the human placental-fetal unit and the fetal liver are able of discriminating between natural and synthetic vitamin E.

The role of vitamin E during different stages of pregnancy, especially during implantation and placental development, is not well understood. α -Tocopherol is probably important in the variability of syncytiotrophoblast cells in the labyrinthine region of the mouse placenta.^{77,78} Kaempfer-Rotzoll et al. reported that α -tocopherol plays a role in the process of implantation and that α -TTP may be necessary for adequate α -tocopherol status of the fetus.⁷² Moreover, it has been demonstrated that oxidative stress in the labyrinthine region of the placenta is inhibited by vitamin E during placental development, with uterine α -TTP, in addition to hepatic α -TTP, playing an important role in this process.⁷⁸

During normal pregnancy, levels of plasma α -tocopherol increase, but in abnormal pregnancies with fetal complications or maternal risks these levels are lower at corresponding gestational ages.⁶³ Newborns have significantly lower plasma vitamin E concentrations than their mothers,⁷⁹ but after standardization of plasma vitamin E concentrations for plasma phospholipids or total lipids these differences were not found to be significant.⁶³ Leger et al.⁸⁰ suggested that vitamin E did not pass efficiently to the newborn

circulation through the placenta. The presence of α -TTP in the placenta suggests a role for α -TTP in the regulation of transfer of tocopherols through the placental barrier.⁸¹ However, unlike vitamin E, vitamin C concentrations are higher in the fetal circulation than in the maternal circulation, and vitamin C is transferred into the human placenta possibly using the glucose carrier.⁸²

VITAMIN E SUPPLEMENTATION AND PREECLAMPSIA

Theoretically, supplementation with antioxidative vitamins C and E should play a significant role in preventing preeclampsia.⁸³ However, this effect has not been confirmed in clinical practice. A summary of various studies evaluating the effects of vitamins C and E supplementation in the prevention for preeclampsia is shown in the Table. Chappell et al.⁸⁴ showed that supplementation with vitamins C and E might be beneficial in the prevention of preeclampsia in women at risk of the disease. However, in a larger study, Poston et al.⁷⁰ failed to confirm such a protective role of vitamin supplementation, and found an increase in the incidence of low birth weight babies exposed to vitamin supplementation. Similarly, Beazley et al.⁸⁵ and Rumbold et al.⁸⁶ conducted clinical trials and could not confirm that supplementation with vitamins C and E during pregnancy reduces the risk of preeclampsia. Rodrigo et al.⁸⁷ suggested that the failure to observe a protective effect may be due to the late initiation of treatment, i.e., after the critical phase of placentation (between 14 and 22 weeks of gestation). Polyzos et al.⁸⁸ concluded that current evidence does support the use of combined vitamin C and E supplementation during pregnancy for the prevention of preeclampsia, although the safety of such supplementation with respect to infant outcome is questionable. Discrepancies in these reports could possibly be related to vitamin E bioavailability among participating women, variability in the regulatory pathways of vitamin E, or to other factors such as the form of vitamin E used in dietary supplementation. Knowing that γ -tocopherol activity decreases after α -tocopherol administration,⁸⁹ and that γ -tocopherol could have a greater effect than α -tocopherol in reducing oxidative processes, vitamin E bioavailability and its isoforms should be assessed in future studies. Furthermore, it is important to note that, in the majority of published studies using vitamin supplementation, plasma levels of vitamin E have not been determined.

Coenzyme Q10 is one of the first respondents in oxidative stress.⁹⁰ It would therefore be relevant to examine the combined effects of coenzyme Q10 with that of vitamins C and E on maternal and infant health.

CONCLUSION

Several recent studies evaluating the effects of α -tocopherol supplementation have failed to show a protective effect, whereas some other studies found adverse effects. Given that supplementation with α -tocopherol decreases the levels of γ -tocopherol, a form of vitamin E with potent protective effects, supplementation with α -tocopherol might not be the best antioxidative procedure. While vitamin E is essential for normal reproductive physiology, an optimal dose-effect relationship has not been determined. In order to correctly assess the effects of exposure to vitamin E, studies correlating plasma and tissue levels to physiological indicators of stress are required. It is likely that vitamin E supplementation is required and effective only when bioavailability is reduced. Further research is thus needed to ascertain if vitamin E supplementation alone or in combination with other supplements during pregnancy could be beneficial to maternal and infant health. It would also be of interest to determine if low birth weight previously found among mothers supplemented with vitamin E could be related to low vitamin E bioavailability, and to examine the combined effects of coenzyme Q10 with that of vitamins C and E on maternal and infant health.

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REFERENCES

1. Stocker R. Vitamin E. *Novartis Found Symp* 2007;282:77–87.
2. Traber MG, Arai H. Molecular mechanisms of vitamin E transport. *Annu Rev Nutr* 1999;19:343–55.
3. Sen CK, Khanna S, Sashwati R. Tocotrienols: vitamin E beyond tocopherols. *Life Sci* 2006;78:2088–98.
4. Sundl I, Murkovic M, Bandoniene D, Winklhofer-Roob BM. Vitamin E content of foods: comparison of results obtained from food composition tables and HPLC analysis. *Clin Nutr* 2007 Feb;26(1):145–53. Epub 2006 Oct 19.
5. Sen CK, Khanna S, Rink C, Roy S. Tocotrienols: the emerging face of natural vitamin E. *Vitam Horm* 2007;76:203–61.
6. Singh U, Devaraj S. Vitamin E: inflammation and atherosclerosis. *Vitam Horm* 2007;76:519–49.
7. Rigotti A. Absorption, transport, and tissue delivery of vitamin E. *Mol Aspects Med* 2007.
8. Burton GJ, Traber MG, Acuff RV, Walters DN, Kayden H, Hughes L, et al. Human plasma and tissue α -tocopherol concentrations in response to supplementation with deuterated natural and synthetic vitamin E. *Am J Clin Nutr* 1998;67:669–84.

9. Fairus S, Nor RM, Cheng HM, Sundram K. Postprandial metabolic fate of tocotrienol-rich vitamin E differs significantly from that of α -tocopherol. *Am J Clin Nutr* 2006;84:835–42.
10. Dietrich M, Traber MG, Jacques PF, Cross CE, Hu Y, Block G. Does γ -tocopherol play a role in the primary prevention of heart disease and cancer? A review. *J Am Coll Nutr* 2006;25(4):292–9.
11. Traber MG, Kayden H. Preferential incorporation of γ -tocopherol vs γ -tocopherol in human lipoproteins. *Am J Clin Nutr* 1989 49:517–26.
12. Goffman FD, Bohme T. Relationship between fatty acid profile and vitamin E content in maize hybrids (*Zea mays* L.). *J Agric Food Chem* 2001;49:4990–4.
13. Kallio H, Yang B, Peippo P. Effects of different origins and harvesting time on vitamin c, tocopherols, and tocotrienols in sea buckthorn (*Hippophae rhamnoides*) berries. *J Agric Food Chem* 2002;50:6136–42.
14. Maranz S, Wiesman Z. Influence of climate on the tocopherol content of shea butter. *J Agric Food Chem* 2004;52:2934–37.
15. Reboul E, Richelle M, Perrot E, Desmoulin-Malezet C, Pirist V, Borel P. Bioaccessibility of carotenoids and vitamin E from their main dietary sources. *J Agric Food Chem* 2006;54:8749–55.
16. Kurilich AC, Tsau GJ, Brown A, Howard L, Klein BP, Jeffery EH, et al. Carotene, tocopherol, and ascorbate contents in Subspecies of *Brassica oleracea*. *J Agric Food Chem* 1999;47:1576–81.
17. Abushita AA, Daood HG, Biacs PA. Change in carotenoids and antioxidant vitamins in tomato as a function of varietal and technological factors. *J Agric Food Chem* 2000;48:2075–81.
18. Goffman FD, Mollers C. Changes in tocopherol and plastoquinone-8 contents in seeds and oil of oilseed rape (*Brassica napus* L.) during storage as influenced by temperature and air oxygen. *J Agric Food Chem* 2000;48:1605–9.
19. Wyatt CJ, Carballido SP, Mendez RO. α - and γ -Tocopherol content of selected foods in the Mexican diet: effect of cooking losses. *J Agric Food Chem* 1998;46:4657–61.
20. Traber MG. Vitamin E regulatory mechanisms. *Annu Rev Nutr* 2007;27:347–62.
21. Reboul E, Klein A, Bietrix F, Gleize B, Malezet-Desmoulin C, Schneider M, et al. Scavenger receptor class B type 1 (SR-B1) is involved in vitamin E transport across the enterocyte. *J Biol Chem* 2006;281(8):4739–45.
22. Traber MG. The ABCs of vitamin E and beta-carotene absorption. *Am J Clin Nutr* 2004;80:3–4.
23. Leonard SW, Good CK, Gugger ET, Traber MG. Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements. *Am J Clin Nutr* 2004;79:86–92.
24. Lodge JK, Hall WL, Jeanes YM, Prottoggento AR. Physiological factors influencing vitamin E biokinetics. *Ann NY Acad Sci* 2004;1031:60–73.
25. Rubinsztein DC, Cohen JC, Berger MG, van der Westhuyzen DR, Coetzee GA, Gevers W. Chylomicron remnant clearance from the plasma is normal in familial hypercholesterolemic homozygotes with defined receptor defects. *J Clin Invest* 1990;86:1306–12.
26. Cooper AD. Hepatic uptake of chylomicron remnants. *J Lipid Res* 1997;38:2173–92.
27. Mustacich DJ, Bruno RS, Traber MG. Vitamin E. *Vitam Horm* 2007;76:1–21.
28. Kiyose C, Saito H, Kaneko K, Hamamura K, Tomioka M, Ueda T, et al. α -Tocopherol affects the urinary and biliary excretion of 2,7,8-trimethyl-2(2'-carboxyethyl)-6-hydroxychroman, γ -tocopherol metabolite, in rats. *Lipids* 2001;36:467–72.
29. Schock BC, Van der Vliet A, Corbacho AM, Leonard SW, Finkelstein E, Valacchi G, et al. Enhanced inflammatory responses in α -tocopherol transfer protein null mice. *Arch Biochem Biophys* 2004;423:162–9.
30. Muller-Schmehl K, Beninde J, Finckh B, Florian S, Dudenhausen JW, Brigelius-Flohe R, et al. Localization of α -tocopherol transfer protein in trophoblast, fetal capillaries endothelium and amnion epithelium of human term placenta. *Free Radic Res* 2004;38:413–20.
31. Tucker JM, Townsend DM. Alpha-tocopherol: roles in prevention and therapy of human disease. *Biomed Pharmacother* 2005;59:380–7.
32. Traber MG, Burton GW, Hamilton RL. Vitamin E trafficking. *Ann NY Acad Sci* 2004;1031:1–12.
33. Landes N, Pfluger P, Kluth D, Birringer M, Ruhl R, Bol G-F, et al. Vitamin E activates gene expression via the pregnane X receptor. *Biochem Pharmacol* 2003;65:269–73.
34. Khanna S, Patel V, Rink C, Roy S, Sen CK. Delivery of orally supplemented α -tocotrienol to vital organs of rats and tocopherol-transport protein deficient mice. *Free Radic Biol Med* 2005;39(10):1310–9.
35. Schultz M, Leist M, Petrzika M, Gassmann B, Brigelius-Flohe R. Novel urinary metabolite of α -tocopherol, 2,5,7,8-tetramethyl-2(2'-carboxyethyl)-hydroxychroman as an indicator of an adequate vitamin E supply? *Am J Clin Nutr* 1995;62:S1527S-S34.
36. Schultz M, Leist M, Elsner A, Brigelius-Flohe R. α -Carboxyethyl-6-hydroxychroman as urinary metabolite of vitamin E. *Methods Enzymol* 1997;282:297–310.
37. Schuelke M, Elsner A, Finckh B, Kohlschutter A, Hubner C, Brigelius-Flohe R. Urinary α -tocopherol metabolites in α -tocopherol transfer protein-deficient patients. *J Lipid Res* 2000;41:1543–51.
38. Hosomi A, Arita M, Sato Y, Kiyose C, Ueda T, Igarashi O, et al. Affinity for α -Tocopherol transfer protein as a determinant of the biological activities of vitamin E analogs. *FEBS Lett* 1997;409:105–8.
39. Hacquebard M, Carpentier YA. Vitamin E: absorption, plasma transport and cell uptake. *Curr Opin Clin Nutr Metab Care* 2005;8:133–8.
40. Mardones P, Rigotti A. Cellular mechanisms of vitamin E uptake: relevance in α -tocopherol metabolism and potential implications for disease. *J Nutr Biochem* 2004;15:252–60.
41. Richelle M, Enslin M, Hager C, Groux M, Tavazzi I, Godin JP, et al. Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. *Am J Clin Nutr* 2004;80:171–7.
42. Iuliano L, Micheletta F, Maranghi M, Frati G, Diczfalusy U, Violi F. Bioavailability of vitamin E as function of food intake in healthy subjects: effects on plasma peroxide-scavenging activity and cholesterol-oxidation products. *Arterioscler Thromb Vasc Biol* 2001;21:e34–e37.
43. Reboul E, Thap S, Perrot E, Amiot M-J, Lairon D, Borel P. Effect of the main dietary antioxidants (carotenoids, γ -tocopherol, polyphenols, and vitamin C) on α -tocopherol absorption. *Eur J Clin Nutr* 2007;61:1167–73.
44. Borel P, Moussa M, Reboul E, Lyan B, Defoort C, Vincent-Baudry S, et al. Human plasma levels of vitamin E and carotenoids are associated with genetic polymorphisms in genes involved in lipid metabolism. *J Nutr* 2007;137:2653–9.
45. Oostenbrug GS, Mensink RP, Al MD, van Houwelingen AC, Hornstra G. Maternal and neonatal plasma antioxidant levels in normal pregnancy, and the relationship with fatty acid unsaturation. *Br J Nutr* 1998;80:67–73.
46. Haga P, Ek J, Kran S. Plasma tocopherol levels and vitamin E/ β -lipoprotein relationships during pregnancy and in cord blood. *Am J Clin Nutr* 1982;36:1200–4.
47. Kaliora AC, Dedoussis GBZ, Schmidt H. Dietary antioxidants in preventing atherogenesis. *Atherosclerosis* 2006;187:1–17.
48. Azzi A. Molecular mechanism of α -tocopherol action. *Free Radic Biol Med* 2007;43:16–21.
49. Banerjee S, Chambers AE, Campbell S. Is vitamin E a safe prophylaxid for preeclampsia? *Am J Obstet Gynecol* 2006;194(5):1228–33.
50. Carr AC, Zhu B-Z, Frei B. Potential antiatherogenic mechanisms of ascorbate (vitamin C) and α -tocopherol (vitamin E). *Circ Res* 2000;87:349–54.

51. Upston JM, Kritharides L, Stocker R. The role of vitamin E in atherosclerosis. *Prog Lipid Res* 2003;42:405–22.
52. Kontush A, Spranger T, Reich A, Baum K, Beisiegel U. Lipophilic antioxidants in blood plasma as markers of atherosclerosis: the role of α -carotene and γ -tocopherol. *Atherosclerosis* 1999;144:117–22.
53. Tessier DM, Khalil A, Trotter L, Fulop T. Effects of vitamin C supplementation on antioxidants and lipid peroxidation markers in elderly subjects with type 2 diabetes. *Arch Gerontol Geriatr* 2008; Article in press.
54. Saldeen T, Li D, Mehta JL. Differential effects of α - and γ -tocopherol on low-density lipoprotein oxidation, superoxide activity, platelet aggregation and arterial thrombogenesis. *J Am Coll Cardiol* 1999;34(4):1208–15.
55. Jiang Q, Elson-Schwab I, Courtemanche C, Ames BN. γ -Tocopherol and its major metabolite, in contrast to α -tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. *Proc Natl Acad Sci USA* 2000;97(21):11494–9.
56. Cooney RV, Franke AA, Harwood PJ, Hatch-Pigott V, Custer LJ, Mordan LJ. γ -Tocopherol detoxification of nitrogen dioxide: Superiority to α -tocopherol. *Proc Natl Acad Sci USA* 1993;90:1771–5.
57. Christen S, Woodall AA, Shigenaga MK, Southwell-Keely PT, Duncan MW, Ames BN. γ -tocopherol traps mutagenic electrophiles such as NO_x and complements α -tocopherol: physiological implications. *Proc Natl Acad Sci USA* 1997;94:3217–22.
58. Huang H-Y, Appel LJ. Supplementation of diets with α -tocopherol reduces serum concentrations of γ - and δ -tocopherol in humans. *J Nutr* 2003;133:3137–40.
59. Devaraj S, Traber MG. γ -Tocopherol, the new vitamin E? *Am J Clin Nutr* 2003;77:530–1.
60. 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.
61. Yoshikawa S, Morinobu T, Hamamura K, Hirahara F, Iwamoto T, Tamai H. The effect of γ -tocopherol administration on α -tocopherol levels and metabolism in humans. *Eur J Clin Nutr* 2005;59:900–5.
62. Eichhorn JCP, Lee R, Dunster C, Basu S, Kelly FJ. α - and γ -Tocopherol plasma and urinary biokinetics following a-topherol supplementation. *Ann NY Acad Sci* 2004;1031:339–40.
63. Brigelius-Flohe R, Kelly FJ, Salonen JT, Neuzil J, Zingg J-M, Azzi A. The European perspective on vitamin E: current knowledge and future research. *Am J Clin Nutr* 2002;76:703–16.
64. Hathcock JN, Azzi A, Blumberg J, Bray T, Dickinson A, Frei B, et al. Vitamins E and C are safe across a broad range of intakes. *Am J Clin Nutr* 2005;81:736–45.
65. Asplund K. Antioxidant vitamins in the prevention of cardiovascular disease: a systematic review. *J Intern Med* 2002;251:372–92.
66. Miller III ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin e supplementation may increase all-cause mortality. *Ann Intern Med* 2005;142:37–46.
67. Investigators T-T. Effects of long-term vitamin E supplementation on cardiovascular events and cancer. *JAMA* 2005;293:1338–47.
68. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention. *JAMA* 2007;297(8):842–57.
69. Chappell LC, Seed PT, Kelly FJ, Briley A, Hunt BJ, Charnock-Jones S, et al. Vitamin C and E supplementation in women at risk of preeclampsia is associated with changes in indices of oxidative stress and placental function. *Am J Obstet Gynecol* 2002;187:777–84.
70. 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(9517):1145–54.
71. Bilodeau J-F, Hubel CA. Current concepts in the use of antioxidants for the treatment of preeclampsia. *J Obstet Gynaecol Can* 2003;25(9):742–50.
72. Kaempf-Rotzoll DE, Igarashi K, Aoki J, Jishage K, Suzuki H, Tamai H, et al. α -Tocopherol transfer protein is specifically localized at the implantation site of pregnant mouse uterus. *Biol Reprod* 2002;67:599–604.
73. Sato Y, Hagiwara K, Arai H, Inoue K. Purification and characterization of the α -tocopherol transfer protein from rat liver. *FEBS Lett* 1991;288:41–5.
74. Dutta-Roy A, Leishman DJ, Gordon MJ, Campbell FM, Duthie GG. Identification of a low molecular mass (14.2kDa) α -tocopherol-binding protein in the cytosol of rat liver and heart. *Biochem Biophys Res Commun* 1993;196(3):1108–12.
75. Arita M, Sato Y, Miyata A, Tanabe T, Takahashi E, Kayden HJ, et al. Human α -tocopherol transfer protein cDNA cloning, expression and chromosomal localization. *Biochem J* 1995;306:437–43.
76. Acuff RV, Dunworth RG, Webb LW, Lane JR. Transport of deuterium-labeled tocopherols during pregnancy. *Am J Clin Nutr* 1998;67:459–64.
77. Jishage K-i, Tachibe T, Ito T, Shibata N, Suzuki S, Mori T, et al. Vitamin E is essential for mouse placentation but not for embryonic development itself. *Biol Reprod* 2005;73:983–7.
78. Jishage K-i, Arita M, Igarashi K, Iwata T, Watanabe M, Ogawa M, et al. α -Tocopherol transfer protein is important for the normal development of placental labyrinthine trophoblasts in mice. *J Biol Chem* 2001;276(3):1669–72. Epub 200 Nov 13.
79. Salle B-L, Delvin E, Claris O. Vitamines liposolubles chez le nourrisson. *Arch Pediatr* 2005;12:1174–9.
80. Leger CL, Dumontier C, Fouret G, Boulot P, Descomps B. A short-term supplementation of pregnant women before delivery does not improve significantly the vitamin E status of neonates-low efficiency of the vitamin E placental transfer. *Int J Vitam Nutr Res* 1998;68:293–9.
81. Kaempf-Rotzoll DE, Horiguchi M, Hashiguchi K, Aoki J, Tamai H, Linderkamp O, et al. Human placental trophoblast cells express a-tocopherol transfer protein. *Placenta* 2003;24:439–44.
82. Rybakowski C, Mohar B, Wohlers S, Leichtwei B H-P, Schroder H. The transport of vitamin C in the isolated human near-term placenta. *Eur J Obstet Gynecol Reprod Biol* 1995;62:107–14.
83. Raijmakers M, Dechend R, Poston L. Oxidative stress and preeclampsia: rationale for antioxidant clinical trials. *Hypertension* 2004;44:374–80.
84. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of preeclampsia in women at increased risk: a randomised trial. *Lancet* 1999;354:810–6.
85. Beazley D, Ahokas R, Livingston J, Griggs M, Sibai BM. Vitamin C and E supplementation in women at high risk for preeclampsia: a double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 2005;192:520–1.
86. Rumbold AR, Crowther CA, Haslam RR, Dekker GA, Robinson JS. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med* 2006;354:1796–806.
87. Rodrigo R, Guichard C, Charles R. Clinical pharmacology and therapeutic use of antioxidant vitamins. *Fundam Clin Pharmacol* 2007;21:111–27.
88. Polyzos NP, Mauri D, Tsappi M, Tzioras S, Kamposioras K, Cortinovis I, et al. Combined vitamin C and E supplementation during pregnancy for preeclampsia prevention: a systematic review. *Obstet Gynecol Surv* 2007;62(3):202–6.
89. Handelman GJ, Machlin IJ, Fitch K, Weiter JJ, Dratz EA. Oral α -tocopherol supplements decrease plasma γ -tocopherol levels in humans. *J Nutr* 1985;115:807–13.
90. Bélanger M-C, Mirault M-E, Dewailly E, Plante M, Berthiaume L, Noël M, et al. Seasonal mercury exposure and oxidant-antioxidant status of James Bay sport fishermen. *Metabolism* 2008;57:630–6.