

signature to patients with immunodeficiency will require further investigation.

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## Vitamins C and E and the Prevention of Preeclampsia

**TO THE EDITOR:** The report by Rumbold et al. on the Australian Collaborative Trial of Supplements (ACTS) and the accompanying editorial by Jeyabalan and Caritis (April 27 issue)<sup>1,2</sup> overlooked a key reason for the lack of effect of vitamin C on the prevention of preeclampsia. Ascorbate administration is based on the hypothesis that different intakes will produce different concentrations and hence outcomes. Because plasma ascorbate concentrations were not reported, we estimated them from known data. On the basis of data from young women who were not pregnant,<sup>3</sup> the placebo and treatment groups in the study by Rumbold et al. probably had similar plasma and tissue ascorbate concentrations. The time–concentration curve for vitamin C is sigmoidal, with plasma concentrations nearing a plateau of 70 to 80  $\mu\text{M}$  at an intake of 200 mg per day.<sup>3,4</sup> Doses of 1 g per day have little effect on plasma or intracellular ascorbate concentrations. Corrections for estimated increased ascorbate needs in pregnancy<sup>5</sup> do not change the conclusion that the concentrations in women in the control group were near saturation.

An appropriate study would measure the effect of ascorbate supplementation in women who were shown to have low plasma ascorbate concentrations at entry. Such subjects exist: among women between the ages of 19 and 30 years in the United States, the lowest 10th percentile receive only 40 mg of vitamin C per day.<sup>5</sup> Plasma measurements and attention to the pharmacokinetics of vitamin C are required before a conclusion can be made regarding whether supplementation has benefit.

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1. 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.
2. Jeyabalan A, Caritis SN. Antioxidants and the prevention of preeclampsia — unresolved issues. *N Engl J Med* 2006;354:1841-3.
3. Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. *Proc Natl Acad Sci U S A* 2001;98:9842-6.
4. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Natl Acad Sci U S A* 1996;93:3704-9.
5. Food and Nutrition Board, Panel on Dietary Antioxidants and Related Compounds. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press, 2000:95-185, 432-7.

**TO THE EDITOR:** Rumbold et al. concluded that vitamin C and E supplementation in nulliparous women did not prevent preeclampsia — findings that concurred with those of our trial in high-risk women.<sup>1</sup> Our study suggested possible harmful effects of these antioxidants in women with clinical risk factors, including an increased frequency of infants with low birth weight (the principal neonatal end point) and an increased use of medication (antihypertensive agents, corticosteroids, and magnesium sulfate). Rumbold et al. also reported an increased requirement for antihypertensive treatment. In exploratory analysis, we found an earlier onset of both preeclampsia and delivery among women who received such supplementation.

Variable definitions make comparisons between studies difficult.<sup>2</sup> We used the definition of preeclampsia — proteinuric hypertension — adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP).<sup>3</sup> Rumbold et al. used a less specific definition of hypertension and one or more of the following: proteinuria, renal insufficiency, liver disease, neurologic

problems, hematologic disturbances, or fetal-growth restriction.<sup>4</sup> Applying the ISSHP definition to the data of Rumbold et al. leads to an increase in the incidence of preeclampsia among women receiving antioxidants, as compared with controls (4.7% vs. 2.8%). We calculated this difference to be significant (risk ratio, 1.70; 95% confidence interval, 1.06 to 2.75;  $P=0.03$ ). To evaluate unexpected findings, a meta-analysis of trials that used similar interventions is invaluable. Further analysis must ensure that similar definitions of end points are used.

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1. 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.
2. Chappell L, Poulton L, Halligan A, Shennan AH. Lack of consistency in research papers over the definition of pre-eclampsia. *Br J Obstet Gynecol* 1999;106:983-5.
3. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of hypertensive disorders of pregnancy: a statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001;20:IX-XIV.
4. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. *Aust N Z J Obstet Gynaecol* 2000;40: 139-55.

**THE AUTHORS REPLY:** Padayatty and Levine highlight the finding that plasma concentrations of vitamin C near a plateau with an intake of 200 mg per day. In our trial, we were not able to measure ascorbate concentrations because of funding limitations. On the basis of questionnaires regarding dietary intake, 13.9% of the participants in our study had a daily intake of vitamin C that was below the 70 mg or more recommended during pregnancy.<sup>1</sup> At least 7.4% of women in the control group would not have reached plasma ascorbate saturation. The effects of antioxidant supplementation on the risk of the primary study outcomes were similar among women with a dietary intake of vitamin C that was below the recommended daily intake and those who received

the recommended intake or more. There remains a need for further assessment of the effects of antioxidant supplementation among women with a low dietary intake of vitamin C.

Briley and colleagues present a summary of the findings of their trial of vitamin C and E supplementation in women with clinical risk factors for preeclampsia. In contrast, our trial involving nulliparous women did not find any effects of supplementation with vitamins C and E on intra-uterine growth restriction (the primary end point) or other measures of infant growth.

A primary outcome for our trial was the development of preeclampsia, for which we used the definition adopted by the Australasian Society for the Study of Hypertension in Pregnancy.<sup>2</sup> Although we agree that variable definitions often make comparisons difficult, there remains a lack of consensus worldwide on the definition of hypertensive disease in pregnancy. Until this issue is resolved, it is important that studies collect sufficient information to allow for a variety of definitions for an assessment of the level of disease. As Briley et al. point out, on the basis of the ISSHP definition, the incidence of preeclampsia in our study was 4.7% in the group receiving supplementation and 2.8% in the control group. However, according to our calculations, this difference is not significant ( $P=0.08$ , with a step-down Sidak adjustment for multiple primary end points). In our trial, supplementation with vitamins C and E during pregnancy did not reduce the risk of preeclampsia in nulliparous women.

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1. National Research Council. Recommended dietary intakes. In: Recommended dietary allowances (RDA). 10th ed. Washington, DC: National Academy of Sciences, 1989. (Accessed August 17, 2006, at <http://www.nal.usda.gov/fnic/dga/rda.pdf>.)
2. Brown MA, Hague WM, Higgins J, et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. *Aust N Z J Obstet Gynaecol* 2000;40: 139-55.