



- **Vitamins C and E: No benefit in pregnancy-associated hypertension**

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Pittsburgh, PA - **The largest study so far** to examine the use of antioxidant doses of vitamins C and E to prevent the complications of pregnancy-associated hypertension, including preeclampsia, **has found no benefit** of this approach [1].

"The bottom line was that within the groups of women we studied, using the same doses of vitamins C and E that were used in all other studies, the groups are virtually superimposable—as far as every primary and secondary outcome, they are almost indistinguishable; **there is no evidence of any benefit**," lead author **Dr James Roberts** (University of Pittsburgh, PA) told **heartwire**. He and his coauthors report their findings in the **April 8, 2010 issue of the New England Journal of Medicine**.

"Women should continue to take prenatal supplements, which have these vitamins in them but at a fraction of the dose," he continued. "But there is no justification for recommending these medications to try to prevent preeclampsia or to try to prevent the complications of preeclampsia at this time," he commented.

No benefit of vitamins on primary outcome or any secondary end points

Roberts explained that the idea that oxidative stress is involved in the development of preeclampsia gained ground during the late 1990s, when a small study involving high-risk women showed a 60% reduction in diagnosis of preeclampsia with supplementation with antioxidant doses of vitamins C and E compared with placebo.

This prompted several other groups to examine this issue, but none were able to replicate the original positive findings.

Roberts said this new study was unique among trials in this field in that they decided the end point would not be a diagnosis of preeclampsia but rather whether the vitamins had any effect on new-onset pregnancy-associated hypertension. This meant they could assess whether the therapy would prevent serious complications rather than merely modify diagnostic findings, he explained.

The multicenter, randomized, double-blind trial conducted between July 2003 and February 2009 involved nulliparous women at low risk for preeclampsia who were randomly assigned to 1000 mg of vitamin C and 400 IU of vitamin E or matching placebo between the ninth

and 16th weeks of pregnancy. Therapy in this study was initiated at an earlier stage of gestation than in any of the previous trials, Roberts noted.

The primary outcome was severe pregnancy-associated hypertension alone or severe or mild hypertension with elevated liver enzymes, thrombocytopenia, elevated serum creatinine levels, medically induced preterm birth, fetal-growth restriction, or perinatal death.

Outcome data were available for 9969 women; there was no significant difference between the vitamin and placebo groups in the rates of the primary outcome (6.1% and 5.7%, respectively; relative risk 1.07) or in the rates of preeclampsia (7.2% and 6.7%; relative risk 1.07), a major secondary outcome.

There was also no evidence of a benefit with vitamin therapy with respect to any of the other prespecified secondary outcomes, the researchers note.

Vitamins associated with slight increase in BP, but not low birth weight

On a positive note, there was no evidence of an excess of low-birth-weight babies among those taking the vitamin supplements in this study, said Roberts, something that was found in a previous trial, the UK **Vitamins in Preeclampsia** (VIP) study.

But researchers did find a slight increase in blood pressure in the women who took vitamins, a finding that was also observed in the VIP study and a similar Australian trial, said Roberts.

"The expectation [was a lowering of BP], but in all three studies not only was there not a reduction, there was actually an excess of higher blood pressure, but not of preeclampsia. So there is something to suggest that either vitamin C or E might have an effect on BP to increase it slightly, but other than that we had no adverse outcomes in our study," Roberts noted.

Vitamins C and E not the answer, but oxidative stress may still play a role

"It's definitely established that the drugs we gave at the doses we gave, when we gave them, did not reduce any of the problems in either high- or low-risk patients when you put all the studies together," Roberts said.

He also noted that these vitamins didn't work in cardiovascular-disease prevention, either: "The cardiovascular literature suggests C and E are not the answer if antioxidants are valuable."

However, he still believes that oxidative stress somehow plays a role in the development of preeclampsia: "People haven't completely given up on the fact that oxidative stress—which is what we were treating with those vitamins—is part of the disease, and we will continue to look for a group that might have benefit."

There are also a couple of trials starting in the UK looking at other antioxidants—selenium, for example, he notes. "Beyond oxidative stress, inflammation is an interesting area, and there is some suggestion that statins may be useful, and there may be a small trial going on."

Second, smaller study replicates findings

A second, smaller study has also found that antioxidant supplementation with the same doses of vitamins C and E did not reduce the rate of preeclampsia or gestational hypertension in almost 2500 women [2]. The study was stopped early, partly because of an increased risk of fetal loss or perinatal death in those treated with the vitamins as opposed to the women who received placebo, although the difference between the two was not statistically significant, say **Dr Hairong Xu** (University of Montreal, QC) and colleagues in their paper in the March 2010 issue of the *American Journal of Obstetrics & Gynecology*.

"Vitamin-C and -E supplementation at the above doses cannot be recommended for pregnant women to prevent adverse pregnancy outcomes including preeclampsia," they conclude.