Antioxidants May Augment Risk of Preeclampsia

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TORONTO — High-dose antioxidant supplementation may be harmful in pregnant women at risk for preeclampsia, according to a study presented at the annual meeting of the Society for Gynecologic Investigation.

The study, comparing placebo with high daily doses of vitamins C (1,000 mg) and E (400 IU) in high-risk women, suggested that high doses of these vitamins conveyed no protective effect against preeclampsia. In fact, these large doses of the two antioxidants were associated with a greater risk of low birth weight, gestational hypertension, and an arterial cord pH less than 7, reported Lucilla Poston, Ph.D., lead author and professor of fetal health at Guy's, King's, and St. Thomas's School of Medicine in London.

The study, fast-tracked to the Lancet, (published online March 30, 2006, doi:10.1016/S0140-6736(06)68433-X) should not be misinterpreted as evidence against regular prenatal vitamins, which include much lower doses of antioxidants, Dr. Poston said in an interview. "There's no suggestion that women taking pregnancy vitamins had any adverse effects," she said.

This is the first study to suggest a risk of high-dose antioxidants in pregnancy, and contrasts with previous work by the same group of investigators that suggested a protective effect of supplementation (Lancet 1999;354:810-6).

"It's quite possible that our previous findings were an error as a result of our small numbers," Dr. Poston said, explaining that the previous study included only 160 women, with an 8% rate of preeclampsia.

She said although it has long been accepted that preeclampsia is associated with oxidative stress, her results suggest that rather than being the cause, oxidative stress may simply be a consequence of the condition. "I'm afraid to say that oxidative stress is probably an innocent bystander in preeclampsia as a result of the disease process," she noted.

The study analyzed 2,395 pregnant women who were at risk for preeclampsia and randomized them at 14-22 weeks' gestation to either high-dose antioxidant therapy or placebo. Subjects who were already taking prenatal vitamins at randomization were allowed to continue taking them.

High-dose antioxidant therapy failed to protect against preeclampsia, which occurred in 15% of the high-dose antioxidant group and 16% of the placebo group.

There also was an association between high-dose antioxidant therapy and low birth weight, defined as less than 2.5 kg. Low-birth-weight babies comprised 28% of the babies in the high-dose antioxidant group, compared with 24% of the placebo group (risk ratio 1.15).

Regarding secondary outcomes, high-dose antioxidant therapy again compared unfavorably with placebo, resulting in higher risks of arterial cord pH less than 7 (RR 2.2), intravenous antihypertensive therapy (RR 1.9), magnesium sulfate therapy for preeclampsia (RR 1.8), gestational hypertension (RR 1.5), and antenatal steroid use (RR 1.4).

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An additional exploratory analysis of the data revealed that high-dose antioxidants were associated with a greater risk of stillbirth (RR 2.7), but a lower risk of death due to immaturity (RR 0.2), although these results could be due to chance, since they were generated from a posthoc analysis, she said.

The harmful potential of large doses of antioxidants is troubling, but consistent with some controversial evidence that high-dose vitamin E has an adverse effect on mortality and morbidity in people with cardiovascular disease, Dr. Poston noted.

"Oxidative stress is involved in a lot of biological processes and it could be there is some fundamental biological process that depends on a little bit of oxidative stress," she said.

The study raises ethical concerns about ongoing antioxidant research in populations that are at risk for preeclampsia, said Dr. Poston. However, she said she has contacted investigators on similar U.S. (National Institutes of Health) and Canadian (Medical Research Council) studies who have decided, after performing interim analyses, to continue their studies.

Another smaller study presented in poster form at the meeting also found no protective effect of high-dose antioxidant therapy against preeclampsia. The study was conducted in a normal, nulliparous population, however, rather than a high-risk group. In fact, there was a trend toward higher preeclampsia rates among women taking high doses of antioxidants (16.7%) compared with those taking placebo (9.7%), said Dr. Heather Mertz, an ob.gyn. at Wake Forest University, Winston-Salem, N.C.

The study of 177 women did show a significant benefit of high-dose antioxidant therapy on neonatal outcome, Dr. Mertz said in an interview. But overall, Dr. Mertz said, her study did not provide enough evidence to counsel patients either for or against high-dose antioxidant therapy during pregnancy. ■

Recurrent Miscarriage? Thrombophilias Unlikely

TORONTO — Recurrent pregnancy loss was not associated with inherited maternal thrombophilias in a prospective study, adding weight to the evidence against screening for such disorders in patients presenting with a history of first-trimester miscarriage.

"It's probably more important to rule out other possible etiological factors," said lead investigator Dr. Sony Sierra in an interview. The study, which she presented at the annual meeting of the Society for Gynecologic Investigation, genotyped 915 Hutterite women for inherited thrombophilia polymorphisms including Factor V Leiden (FVL) Arg506Gln, the MTHFR Ala222Val, and the prothrombin G20210A variants.

A total of 141 women were identified with inherited thrombophilias and were prospectively followed through 342 pregnancies. The rate of fetal loss, defined as loss at or before 20 weeks of gestation, was 16% in the cohort, which is comparable to the rate found in the general population, reported Dr. Sierra, of the department of obstetrics and gynecology at the University of British Columbia in Vancouver. "We also found that the majority of miscarriages occurred at less than 12 weeks—and since there has been evidence to suggest that thrombophilias could be associated with later fetal loss beyond 20 weeks, our findings just lend further support to the data that for early miscarriage there is no significant association," she said.

Genotype analysis was performed on a subset of 72 live offspring and compared with maternal and paternal genotyping. The analysis revealed an expected transmission rate of the MTHFR Val allele to offspring; however, there were significantly fewer children born with the FVL allele (28) than expected (37). (There were no parental carriers of the prothrombin 20210A allele.)

There may be a "selection against inherited thrombophilic variants during embryogenesis," she said. ■

Periodontal Disease and High Levels Of CRP May Predict Preeclampsia

TORONTO — A combination of maternal periodontal disease and high levels of maternal C-reactive protein is associated with significantly more risk of preeclampsia than either risk factor alone, according to a new analysis of the Oral Conditions and Pregnancy Study.

"There seems to be some type of synergy when both are combined," said Dr. Michael S. Ruma, who presented the findings at the annual meeting of the Society for Gynecologic Investigation.

A secondary analysis of 775 healthy pregnant women who had oral examinations and C-reactive protein (CRP) levels measured at enrollment (less than 26 weeks' gestation) found that preeclampsia was more common in those with high CRP levels alone (OR 2.6), and those with moderate to severe periodontal disease (PD) alone (OR 2.0)—but a combination of high CRP levels and moderate to severe PD increased the odds ratio to 7.0.

A total of 31 women (4%) developed preeclampsia in the cohort. The rate of preeclampsia was greater among women with a high CRP level (above the 75th percentile) than for women with a low CRP level (at or below the 75th percentile): 7% and 3%, respectively. The addition of mild PD to the elevated CRP level significantly increased the risk of preeclampsia from an odds ratio of 2.6 to 6.0 and moderate to severe PD increased it further (OR 7.0).

"Maternal systemic inflammation may be in the causal pathway between periodontal disease and the development of preeclampsia," said Dr. Ruma of the University of North Carolina at Chapel Hill. However, he said, future research is required to further understand this phenomenon. "Both periodontitis and preeclampsia are multifactorial, but the implication is that inflammation in the mother is leading to systemic disease," he said in an interview.

A separate study presented at the meeting suggests that such maternal inflammation may also be transferred to the fetus—particularly in the setting of maternal smoking.

In a study of 277 women, Dr. John P. Newnham of the Women and Infants Research Foundation at King Edward Memorial Hospital in Perth, Western Australia, and his colleagues found that 12% of women with PD had babies who were small for gestational age (SGA), compared with 2% of women who had healthy gums ("Gum Disease Again Tied to Pregnancy Outcomes," FAMILY PRACTICE NEWS, Sept. 1, 2005, p. 50). Further analysis of this study, which was presented at the meeting, found this effect is significantly increased (25%) in women who smoke. Additionally, the researchers found that in smokers, both with and without PD, inflammatory markers (CRP and tumor necrosis factor–α) were significantly elevated in umbilical cord blood, indicating an inflammatory response in the fetus.

"The thing I found absolutely fascinating was this marked inflammation in the fetus at birth as a result of the woman smoking in pregnancy—and PD added further to it," Dr. Newnham said in an interview. "Smoking not only increases the risk of PD, which everyone has known for a long time, but smoking increased the inflammatory markers in the cord blood and PD added to this."

Although the absence of PD is associated with better obstetric outcomes, it is not known whether treating PD during pregnancy is beneficial or harmful, said Dr. Newnham. "We are in equipoise. We know inflamed periodontal tissue can release cytokines and prostaglandins," he said, leading some to hypothesize that the treatment of PD could temporarily increase maternal systemic inflammation. ■