

# Vitamins C and E Linked To Gestational Events

*A metaanalysis tied high-dose supplements to greater risks of gestational hypertension and stillbirth.*

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LISBON — A metaanalysis of results from two major trials of prenatal supplementation with high dosages of vitamins C and E has raised concern about possible adverse effects, such as an increased risk of stillbirths and of gestational hypertension.

More stillbirths are “a worry, but it is an exploratory analysis. We’ll need to look at the results from other studies” that are still in progress, Dr. Andrew H. Shennan said at the 15th World Congress of the International Society for the Study of Hypertension in Pregnancy.

Although results from the two recent trials—which together involved more than 4,000 women—showed that high dosages of vitamin C and E supplements had no benefit for preventing preeclampsia and may have caused harm, experts continued to endorse the underlying hypothesis that treatment with one or more antioxidant agents might prevent preeclampsia.

“There is a sound academic basis to think that oxidative stress plays a role in preeclampsia,” said Dr. Lucilla Poston, a professor in the maternal and fetal research unit at King’s College London, and co-principle investigator for one of the trials.

“We don’t want people to go away thinking that this is the end of oxidative stress in preeclampsia. Preeclampsia is a very rapid situation, with accelerated oxidative stress. We need to think about the etiology of oxidative stress and the enzymes that produce superoxides,” Dr. Poston said.

The Vitamins in Preeclampsia (VIP) trial enrolled about 2,400 pregnant women at week 14-21 gestational age who were at high risk for preeclampsia at 26 centers, 25 of them in the United Kingdom. The women were randomized to placebo or daily supplementation with 1 g vitamin C and 400 IU vitamin E daily through delivery. The high dosages of the two vitamins contrast with the content of a typical prenatal vitamin, which often contains 120 mg of vitamin C and 30 IU of vitamin E.

The primary end point was preeclampsia incidence. To qualify as high risk, women had to have at least one condition from a prespecified list that included a history of preeclampsia before 37 weeks in the preceding pregnancy, gestational hypertension, preconception diabetes, body mass index (kg/m<sup>2</sup>) of at least 30 at first antenatal examination, renal disease, and abnormal uterine artery Doppler waveform analysis.

Preeclampsia occurred in 15% of women on the vitamin supplement and in 16% of those on placebo, a nonsignificant difference (Lancet 2006;367:1145-54).

The second trial reported in April was the Australian Collaborative Trial of Supplements (ACTS), which enrolled 1,877 pregnant women at 14-22 weeks gestational age who were at low risk for preeclampsia, at nine centers in Australia. The vitamin supplement dosages were the same as the dosages in the VIP trial; the primary outcomes were also similar. To focus on low-risk women, the study enrolled only nulliparous women with singleton pregnancies who were normotensive; the study also had other exclusion criteria. The average BMI of women in the study was 24.

The rate of preeclampsia was 6% in the supplement group and 5% in the control group, a difference that did not reach statistical significance (N. Engl. J. Med. 2006;354:1796-806).

Although results from both studies put to rest the idea of high-dosage prenatal vitamin C and E supplements, many pregnant women are currently taking these vitamins at high dosages, said Dr. Shennan, a pro-



Many pregnant women are taking vitamins C and E at high dosages, even though trials have shown there is no benefit.

fessor of obstetrics at King’s College London and the second principal investigator for the VIP trial. That fact is especially worrying given the suggestion of harm from these dosages in a metaanalysis that included the VIP and ACTS trials as well as two small, earlier studies. All four studies used the same supplement dosages, and they together involved more than 4,500 pregnant women.

Overall, women in the vitamin group had a roughly 50% higher rate of gestational hypertension, and a nearly twofold higher rate of both treatment with an antihypertensive agent and treatment with magnesium sulfate for preeclampsia, Dr. Shennan reported.

The rate of stillbirths was also twice as high in women who received vitamin supplements compared with those in the control group. All of the differences were statistically significant. ■

## DRUGS, PREGNANCY, AND LACTATION

### Morphine Poisoning via Breast Milk

Last month, my associates and I published a case report of an apparently healthy full-term newborn who died at 13 days from morphine poisoning. The cause was determined to be a genetic polymorphism in the mother, which made her an ultrarapid metabolizer of codeine to morphine, via cytochrome P450 2D6 (CYP2D6).

The coroner investigating the death contacted us after detecting an extremely high blood morphine level in the baby, because the mother had been taking codeine for episiotomy pain and had been breast-feeding. We suspected the mother might have the polymorphism, identified in recent years in a population subgroup. In one case involving ultrarapid CYP2D6 metabolism, a healthy man almost died from morphine poisoning when he received codeine for dental pain (N. Engl. J. Med. 2004;351:2827-31).

Genetic testing of the mother, father, baby, and extended family members identified the mother (and maternal grandmother) as ultrarapid CYP2D6 metabolizers, but not the baby. Frozen breast milk had a morphine level far higher than described in the literature: 87 ng/mL, vs. the typical level of 1.9-20.5 ng/mL associated with maternal doses of 60 mg of codeine every 6 hours (Lancet 2006;368:704).

Overall, there has been the perception that codeine is safe for the baby during breast-feeding. The few studies that have evaluated breast milk in women taking codeine have not found high morphine levels, and the American Academy of Pediatrics and other authoritative bodies list codeine as compatible with breast-feeding.

In most cases, this remains true. But considering the common practice of prescribing codeine for pain after episiotomy or cesarean section, many babies may be at risk. The prevalence of ultrarapid metabolizer status ranges from 1% in Denmark and Finland to 10% in Greece and Portugal to 29% in Ethiopia.

A genetic test is commercially available, but it is expensive and is currently not routinely performed. Other options all have pros and cons. One could withhold codeine in the postpartum period, but codeine is sometimes clearly needed for pain. Using a non-steroidal anti-inflammatory drug and avoiding codeine when breast-feeding eliminates the risk of toxicity in the baby, but may not adequately control pain. Using a lower dose of codeine minimizes potential toxicity to the baby, but may not provide sufficient pain control for the mother, and the dose could still be too high if she is an

ultrarapid metabolizer. Another option is to avoid breast-feeding while taking codeine, but the baby would lose the benefits of breast-feeding.

In our case the mother took codeine until the child died at 13 days, which is longer than usual. This suggests that use for no more than 2-3 days is advisable. In retrospect, there were clinical signs hinting that the mother was an ultrarapid metabolizer: Despite being on a low dose of codeine, in combination with paracetamol, she was somnolent and constipated, and the dose had to be reduced on the second day of treatment.

Be alert for signs and symptoms suggesting that a patient is an ultrarapid metabolizer, including somnolence, sleepiness, dizziness, and constipation. The metabolism to morphine by CYP2D6 is responsible for most of the analgesic and CNS

depressant effects of codeine.

Why have cases like this one not been previously reported? I suspect such cases may not be as rare as we thought, but not all the cases are as tragic because the mothers do not take codeine for as long a time. For example, in a paper we published more than a decade ago on outcomes in babies exposed to drugs in breast milk, 25 women reported taking codeine while breast-feeding, and in five cases their babies were described as being sleepy. An abstract from a 1984 meeting described apnea in premature babies who were being breast-fed, which resolved as soon as their mothers stopped taking codeine. Interestingly, their symptoms began at about day 7, which was also the case in our report, suggesting it takes time for morphine to accumulate in the milk to dangerous levels.

Eventually, this is the type of pharmacogenetic information everyone will be aware of and will have available when presenting for medical care. For now, we are conducting a large case-control pharmacogenetic study funded by Genome Canada on babies who were breast-fed while the mother was using codeine to better define the scope of this issue.

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