

MEGA-DOSE VITAMIN C AND E IN PREVENTING FASD: THE DECISION TO TERMINATE THE STUDY PREMATURELY

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ABSTRACT

Since 2004 we have been conducting a randomized control double blind trial on the favourable effect of mega-vitamin C and E in pregnant women with heavy alcohol exposure. The study was terminated in the summer of 2006 due to new evidence showing intrauterine growth restriction caused by such treatment in women with pre-eclampsia.

FASD (fetal alcohol spectrum disorder) affects 1 of 100 children.¹ As FASD results from alcohol exposure during pregnancy mothers are advised to discontinue drinking when planning pregnancy. However, a large number of pregnancies are unplanned or unrecognized until fairly late in gestation. In the 1988 National Maternal and Infant Health Survey on drinking by pregnant women Floyd *et al.* reported that 45% women surveyed reported consuming alcohol during the three months before finding out they were pregnant.² As such, providing a means of ameliorating the damage inflicted by maternal use of alcohol is of important interest.

One of the mechanisms believed to cause FASD is oxidative damage generated by oxidative stress which occurs during alcohol exposure. Previous experimental studies have demonstrated that ethanol damage to neural cells can be attenuated by treatment with antioxidants.^{3,4} In addition, previous studies have also documented the potential benefits of mega-dose antioxidant vitamin supplementation with vitamin C and E in diabetic and pre-eclamptic women.^{5,6} As a result of these previous studies, we designed the EViCE (Effectiveness of Vitamin C and E in alcohol exposed pregnancies) study to examine the effectiveness of mega-dosing of Vitamin C and E in mitigating the effects of ethanol in alcohol exposed women. This was a randomized control study initiated in the fall of 2004. In the study, women with alcohol-exposed pregnancies were randomized into three groups: vitamin, placebo,

and counseling only. Women assigned to the vitamin group received a 1000mg vitamin C, 400IU vitamin E, and a prenatal multivitamin containing folic acid. Women assigned to the placebo group received two placebos and a prenatal multivitamin containing folic acid. Women assigned to the counseling group did not receive any vitamin therapy but were advised to take prenatal multivitamins containing folic acid. The rationale for including a counseling group was to examine the effect of usual care.

As part of the ethicality of any human study, it is critical to follow up the world experience to see whether new knowledge may affect the conduct of the trial. The turning point of the EViCE trial arose with the publication of pre-eclampsia trials using vitamin C and E.^{7,8} The trial of vitamin C and E by Rumbold *et al.* suggested that supplementation with these vitamins did not reduce the risk of pre-eclampsia.⁷ More important, however, was the randomized control trial published by Poston *et al.* where women randomized to receive antioxidants delivered more low birth weight babies compared to the placebo arm.⁸ The study by Poston *et al.* investigated the effects of 1000mg vitamin C and 400IU RRR-vitamin E. Of the 2,395 patients analyzed, despite similar incidences of pre-eclampsia (RR 0.97 [95% CI 0.80-1.17]), babies born to women who took antioxidants had lower birth weight (RR 1.15 [96% CI 1.02-1.30]). This difference could not be accounted for by gestational age. These findings have resulted in

major changes in the research involving pregnant women receiving mega-doses for vitamin C and E and led us to assess the viability of our trial. In August 2006, a safety committee meeting was convened to review the justification of continuing the trial. The committee was comprised of the study investigator as an observer, neurologist, toxicologist, and two obstetricians, one of whom coordinated a vitamin C and E study for pre-eclampsia. Data regarding birth outcomes of the EViCE study were presented to the safety committee. There were no cases of low birth weight babies observed in our trial. The committee reviewed the decision on a Toronto-based vitamin C and vitamin E study in pre-eclampsia which was also terminated. The committee concluded that recruitment into the trial should be discontinued and that the ongoing participants be followed to the designated study end points.

A previous review of vitamin C supplementation during pregnancy did not reveal any adverse fetal effects.⁹ Similarly a review of vitamin E supplementation did not report any adverse effects.^{10,11} However, a recent prospective observational study conducted by our group in pregnant women supplementing with mega-doses of vitamin E, detected an apparent decrease in mean birth weight that could not be explained by other variables including maternal age, gestational age, and smoking.¹² The safety committee concluded that the principle of equipoise was violated with the results of a new randomized study showing vitamin C and vitamin E to be associated with a clinically-significant intrauterine growth retardation in pre-eclampsia.

We subsequently encountered a previous trial in pregnancy that was suspended prior to its completion—a placebo-controlled trial of women receiving nicotine patches.¹³ One mother reported excess symptoms associated with withdrawal and excess fetal movements when she used her study medication. It was revealed that she had been randomly assigned to placebo, hence exposing the fetus to the risk of nicotine withdrawal.

Our study is being renewed with a different design omitting the placebo arm and adding a dose-escalating strategy. Together these trials demonstrate the importance of continuous monitoring of studies for unseen adverse effects,

especially in a population as vulnerable as pregnant alcoholic women.

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