

## LETTER TO THE EDITOR

# Combined Vitamin C and E supplementation for Preeclampsia: No Significant Effect But Significant Heterogeneity?

Dear Editor,

We have read with interest the recent meta-analysis by Rahimi et al. (1). The results of this meta-analysis are in accordance with a previous meta-analysis (2) regarding the effects of the combination of vitamin C and E on preeclampsia prevention. Nonetheless, despite the uniformity of results between these two meta-analyses, the updated results of the meta-analysis by Rahimi et al. (1) revealed a statistical heterogeneity for the incidence of preeclampsia in the comparison of vitamin combination versus placebo. The authors performed a sensitivity analysis by excluding two of the trials (3,4) on account of the fact that the supplementation was initiated after 18 weeks of gestation and no statistical heterogeneity was observed for the remaining five studies.

Indeed, according to the meta-analysis plot, these two trials appear to have contributed highly to the observed heterogeneity. However, the delay in the initiation of the antioxidant treatment, later than the 18th week of gestation as claimed by the authors, is not likely to be the reason for the diverse outcomes among these two trials and the other trials. Delaying the onset of vitamin supplementation could have only contributed to a detrimental effect of the vitamin regimen on the prevention of preeclampsia and, consequently, the result of these trials should have favored the placebo arm. On the contrary, in both of the trials statistically significant lower rate of preeclampsia has been observed in the vitamin arm.

If we would like to give a reasonable explanation for this heterogeneity we should recall the potential differences in the antioxidant status of the women enrolled. Antioxidant supplementation in women with low antioxidant status has been correlated with better maternal and perinatal outcomes as compared to the control group (5). Therefore, considering that both trials (3,4) have been conducted in Iran and previous reports have underlined inadequate vitamin C intake in the urban areas of Iran as compared to the rural areas (6), it may be likely that vitamins may have a beneficial effect on the incidence of preeclampsia in these populations owing to the possible lower antioxidant status of the Iranian patients.

Another explanation may be the fact that one of the trials appears, according to its abstract, to be a case control and not a randomized controlled trial (3). We were unable to retrieve the full text of this trial; however, based on its

abstract it is very likely to be a case control rather than a randomized controlled trial. Considering that results from observational studies are not high-quality evidence and are prone to biases, mainly because of the failure to adjust for potential confounding factors, possibly in this trial the effect of vitamin supplementation on the incidence of preeclampsia may be flawed.

Finally, a feasible explanation may be a local literature bias, known as a “reverse tower of Babel bias,” which has been previously reported (7). In certain cases locally produced and published literature is spuriously statistically significant (7,8), and this may be the case with these two trials.

In conclusion, sources of bias must always be identified in meta-analyses and statistical heterogeneity must be interpreted with caution.

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