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SUPPLEMENTATION WITH VITAMINS C AND E DURING PREGNANCY FOR THE PREVENTION OF PREECLAMPSIA AND OTHER ADVERSE MATERNAL AND PERINATAL OUTCOMES: A SYSTEMATIC REVIEW AND METAANALYSIS

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Abstract

OBJECTIVE—To determine whether supplementation with vitamins C and E during pregnancy reduces the risk of preeclampsia and other adverse maternal and perinatal outcomes.

STUDY DESIGN—Systematic review and metaanalysis of randomized controlled trials.

RESULTS—Nine trials involving a total of 19,810 women were included. Overall, there were no significant differences between the vitamin and placebo groups in the risk of preeclampsia (9.6% versus 9.6%; relative risk 1.00, 95% confidence interval 0.92–1.09). Similar results were obtained when subgroup analyses were restricted to women at high risk or low/moderate risk for preeclampsia. Women supplemented with vitamins C and E were at increased risk of developing gestational hypertension and premature rupture of membranes, and a decreased risk of abruptio placentae. There were no significant differences between the vitamin and placebo groups in the risk of other adverse maternal or fetal/perinatal outcomes.

CONCLUSION—Supplementation with vitamins C and E during pregnancy does not prevent preeclampsia.

Keywords

Antioxidants; gestational hypertension; abruptio placentae; premature rupture of membranes

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INTRODUCTION

Preeclampsia complicates 1.3% to 6.7% of all pregnancies and remains a major cause of maternal and perinatal morbidity and mortality worldwide.^{1,2} Preeclampsia has been considered a two-stage disorder in which a poorly perfused placenta (Stage 1), due to inadequate remodeling of the spiral arteries supplying the intervillous space, produces factor(s) leading to the clinical manifestations of preeclampsia (Stage 2).³ Stage 1 is not sufficient to cause the maternal syndrome but interacts with maternal factors (genetic, behavioral or environmental) to result in Stage 2. Oxidative stress of the placenta is considered to be a key intermediary step in the pathogenesis of preeclampsia.^{4–7} This hypothesis is supported by strong evidence of increased concentrations of biomarkers for oxidative stress and decreased concentrations of antioxidants such as vitamins C and E in the serum and tissues of women with established preeclampsia compared to those without this disorder.⁸

Antioxidants are important in maintaining cellular function in normal pregnancy and act through inhibition of peroxidation, thus protecting enzymes and proteins as well as cell integrity.^{9,10} Vitamins C and E are antioxidants: vitamin C scavenges free radicals in the aqueous phase,¹¹ whereas vitamin E acts *in vivo* to prevent lipid peroxidation,¹² protecting against oxidative stress-related damage of cellular and intracellular structures. In addition to acting as a scavenger of free radicals, vitamin C can interact with the tocopheroxyl radical and regenerate reduced tocopherol.¹³ Furthermore, vitamins C and E are able to interact with glutathione-related enzymes to control the production of lipid peroxidation products.¹³ These observations led to the hypothesis that early supplementation with antioxidants could be effective in decreasing oxidative stress and improving vascular endothelial function, thereby preventing or ameliorating the course of preeclampsia.

In 1999, Chappell et al.¹⁴ published the results of a randomized controlled trial in which 283 women (identified as being at increased risk for preeclampsia because of an abnormal two-stage uterine artery Doppler analysis or a previous history of preeclampsia) were randomly assigned to receive vitamins C and E or placebo at 16–22 weeks' gestation. Vitamin supplementation was associated with a significant reduction in the maternal concentrations of biomarkers for preeclampsia [plasminogen-activator inhibitor (PAI)-1-to-PAI-2 ratio] and a 54% reduction in the risk of preeclampsia. These encouraging results led to the performance of several recently published larger trials involving women at both high risk and low/moderate risk for the disorder.^{15–24} Questions concerning the efficacy and safety of administering vitamins C and E during pregnancy for preventing preeclampsia have been raised.^{25–27}

We conducted a systematic review and metaanalysis of all available randomized controlled trials to determine the efficacy and safety of supplementation with vitamins C and E during pregnancy for the prevention of preeclampsia and other adverse maternal and perinatal outcomes.

MATERIAL AND METHODS

The study was conducted following a prospectively prepared protocol and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for meta-analysis of randomized controlled trials.²⁸

Data sources and searches

We searched MEDLINE, EMBASE, CINAHL, and LILACS (all from inception to November 30, 2010), the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) (1960 to November 30, 2010), ISI Web of Science (<http://www.isiknowledge.com>) (1960 to November 30, 2010), Research Registers of ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.anzctr.org.au, <http://www.nihr.ac.uk>, and www.umin.ac.jp/ctr), and Google scholar using a combination of keywords and text words related to *vitamins C and E* or *antioxidants*, and *preeclampsia*. Proceedings of the Society for Maternal-Fetal Medicine and international meetings on preeclampsia, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. No language restrictions were used.

Study selection

We included randomized controlled trials that compared supplementation with vitamins C and E during pregnancy with placebo or no supplementation and whose primary aim was to prevent preeclampsia or if the primary aim was otherwise but data on preeclampsia were reported. Trials were excluded if: 1) they were quasi-randomized; 2) they evaluated vitamins C or E alone; 3) they evaluated vitamins C and E combined with other vitamins or nutritional supplements; 4) they did not report clinical outcomes; or 5) they evaluated vitamins C and E in women with established preeclampsia or premature rupture of membranes (PROM). Trials were classified according to women's risk status for preeclampsia. Pregnant women were considered to be at high risk for preeclampsia if they had one or more of the following: previous preeclampsia, eclampsia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, chronic hypertension, renal disease, pregestational diabetes, a body mass index (BMI) ≥ 30 kg/m² in the first pregnancy, abnormal uterine artery Doppler velocimetry, antiphospholipid syndrome or multiple pregnancy. Pregnant women were considered at low/moderate risk for preeclampsia if they were nulliparous and did not meet any of the above mentioned criteria for high risk. We subdivided the trials as a function of the risk for preeclampsia in order to determine if the efficacy of vitamins C and E might vary according to the presence or absence of clinical risk factors of women participating in the trials.

All published studies deemed suitable were retrieved and reviewed independently by two authors (A.C-A. and J.P.K.) to determine inclusion. Disagreements were resolved through consensus.

Outcome measures

The primary outcome of interest was preeclampsia. Secondary maternal outcomes included severe preeclampsia, eclampsia, HELLP syndrome, gestational hypertension, severe gestational hypertension, use of any antihypertensive therapy, antenatal hospitalization for hypertension, use of magnesium sulfate, abruptio placentae, pulmonary edema, admission to intensive care unit, maternal death, PROM, and preterm PROM (PPROM). Secondary fetal and perinatal outcomes included low birth weight, small for gestational age, preterm birth <37 weeks, fetal death <24 weeks, stillbirth, neonatal death, perinatal mortality, congenital malformation, admission to the neonatal intensive care unit (NICU), respiratory distress syndrome, necrotizing enterocolitis, neonatal sepsis, retinopathy of prematurity, intraventricular hemorrhage (all grades), grade III/IV intraventricular hemorrhage, periventricular leukomalacia, neonatal seizures, use of surfactant, mechanical ventilation, and chronic lung disease.

Assessment of risk of bias in included studies

The risk of bias in each trial included in this review was assessed individually by two reviewers (A.C-A. and J.P.K.) not associated with any of the trials. When differences in assessment of risk of bias existed, the differences were resolved by consensus. We assessed the risk of bias using the criteria recently outlined in the Cochrane Handbook for Systematic Reviews of Interventions.²⁹ Six domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) sequence generation; 2) allocation concealment; 3) blinding of participants, clinical staff and outcome assessors; 4) incomplete outcome data; 5) selective outcome reporting; and 6) other sources of bias. We assessed the risk of bias by answering a pre-specified questionnaire about the adequacy of the study in relation to the entry, such that a judgment of “Yes” indicates low risk of bias, “No” indicates high risk of bias, and “Unclear” indicates unclear or unknown risk of bias.

Data extraction

Two authors (A.C-A. and J.P.K.) extracted data from each study on participants (inclusion and exclusion criteria, number of women and fetuses/infants in randomized groups, baseline characteristics, and country and date of recruitment), study characteristics (randomization procedure, concealment allocation method, blinding of clinicians, women and outcome assessors, completeness of outcome data for each outcome, including attrition and exclusions from the analysis, and intention to treat analysis), details of intervention (aim, daily dose of vitamins, gestational age at trial entry, and duration of treatment), and outcomes (number of outcome events/total number). In an attempt to obtain additional data, we contacted four authors by e-mail of whom three responded. Disagreements in extracted data were resolved by discussion among reviewers.

Statistical analysis

Statistical analysis was performed following the guidelines of the Cochrane Collaboration.³⁰ We analyzed outcomes on an intention-to-treat basis. If this was not clear from the original article, we carried out re-analysis when possible. If data for similar outcomes from two or more separate studies were available, we combined the data in a meta-analysis and calculated a summary relative risk (RR) with associated 95% confidence interval (CI). Heterogeneity of the results among studies was tested with the quantity I^2 , which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.³¹ A value of 0% indicates no observed heterogeneity, whereas I^2 values of 50% or more indicate a substantial level of heterogeneity.³¹ We planned to pool data across studies using the fixed-effects models if substantial statistical heterogeneity was not present. Random-effects models were used to pool data across studies if I^2 values were $\geq 50\%$ and possible causes of heterogeneity were explored by performing subgroup analyses for the main outcomes according to study characteristics. A predefined sensitivity analysis was performed, by excluding trials with any risk of bias, in order to explore the impact of study quality on the effect size for the primary outcome.

Further subgroup analyses were planned to assess the primary outcome in women who were at low/moderate and high risk for preeclampsia. In addition, in women who were at high risk for developing preeclampsia, we assessed the primary outcome according to the presence of the following risk factors: previous preeclampsia, chronic hypertension, pregestational diabetes, multiple pregnancy, BMI ≥ 30 kg/m² in the first pregnancy, abnormal uterine artery Doppler velocimetry, chronic renal disease, and antiphospholipid syndrome.

The number needed to treat (NNT) for benefit or harm with their 95% CIs was calculated for outcomes for which there was a statistically significant reduction or increase in risk

difference.³² NNT was computed from the results of meta-analysis of relative risks as follows:

$$\text{NNT} = \left| \frac{1}{\text{Control group event rate} \times (1 - \text{relative risk})} \right|$$

NNT for an additional beneficial outcome is the number of women who need to be treated with vitamins C and E rather than with placebo to prevent one case of an adverse maternal/perinatal outcome. The NNT for an additional harmful outcome is the number of women who need to be treated with vitamins C and E rather than with placebo for one additional woman or infant to be harmed by an adverse event.

We assessed publication and related biases visually by examining the symmetry of funnel plots and statistically by using the Egger test.³³ The larger the deviation of the intercept of the regression line from zero, the greater the asymmetry and the more likely that the meta-analysis would yield biased estimates of effect. As suggested by Egger, we considered $P < 0.1$ to indicate significant asymmetry.

Analyses were performed with the Review Manager (RevMan) software version 5.0.23 (The Nordic Cochrane Centre, Denmark), and StatsDirect version 2.7.8 (StatsDirect Ltd, United Kingdom).

RESULTS

Study selection, details, and quality

The searches yielded 2,794 citations, of which 29 were considered relevant (Figure 1). Twenty studies were excluded, mainly because they evaluated vitamins C and/or E combined with other vitamins or nutritional supplements (35%), evaluated vitamin C alone (25%), or included women with established preeclampsia (20%). References for excluded studies can be obtained from the authors. Nine studies, including 19,810 women and 20,533 fetuses/infants, fulfilled inclusion criteria of which 6 (5,601 women) evaluated vitamins C and E in women at high risk of preeclampsia,^{14–16,18,19,22} 2 (11,846 women) evaluated vitamins in women at low/moderate risk,^{17,21} and one (2,363 women) evaluated vitamins in women at both high and low/moderate risk.²⁰ Interrater agreement for study inclusion was 100% (κ , 1.00). Two studies^{18,21} reported data on the effect of vitamin C and E supplementation on the risk of PROM and/or PPRM in additional reports.^{23,24}

The main characteristics of studies included in this meta-analysis are presented in Table 1. Three studies were performed in the United Kingdom,^{14,16,22} 2 in the United States,^{15,21} 1 each in Australia¹⁷ and Brazil,¹⁸ 1 in Canada and Mexico,²⁰ and the remaining study was conducted in 4 developing countries.¹⁹ Overall, 68% of women included in this review ($n=13,525$) were at low/moderate risk of developing preeclampsia at trial entry. 32% percent of women ($n=6,285$) were considered high risk. Three trials recruited nulliparous women with a singleton pregnancy^{17,20,21} and 7^{14–16,18,19,20,22} included women with at least one of the following risk factors for preeclampsia: preeclampsia in the preceding pregnancy or eclampsia or HELLP syndrome in any previous pregnancy,^{14,16,19} preeclampsia in any previous pregnancy,^{15,18,20} chronic hypertension,^{15,16,18–20} pregestational diabetes,^{15,16,19,20,22} multiple pregnancy,^{15,16,20} primiparity with body mass index (BMI) 30 kg/m^2 ,^{16,19} abnormal uterine artery Doppler velocimetry,^{14,16,19} chronic renal disease^{16,19} or antiphospholipid syndrome.^{16,19} The sample size ranged from 100¹⁵ to 9,969²¹ women (median, 1,355¹⁹). The total daily dose of vitamins C and E used in all of the included trials was 1000 mg and 400 International units, respectively. Four trials

recruited women between 14 and 20–22 weeks' gestation,^{15–17,19} 3 recruited women before 20 weeks' gestation,^{18,20,21} and the remaining 2 studies recruited women between 16 to 22 weeks' gestation¹⁴ and 8 to 22 weeks' gestation.²² Five studies^{16,17,19,21,22} reported that participating women received study medication from enrollment until delivery, one¹⁸ reported that women received study medication from enrollment until delivery or until the diagnosis of preeclampsia, and 3^{14,15,20} did not report on duration of intervention. Preeclampsia was defined as gestational hypertension occurring after 20 weeks' gestation plus proteinuria (300 mg/24 hours or 2+ on dipstick testing,^{14,16,18,20} or 300 mg/24 hours or 1+ on dipstick testing,^{19,22} or 300 mg/24 hours or 2+ on dipstick testing or a protein/creatinine ratio ≥ 0.35 ²¹) in 7 trials. In the study by Rumbold et al.,¹⁷ preeclampsia was defined as gestational hypertension occurring after 20 weeks' gestation and one or more of the following: proteinuria, renal insufficiency, liver disease, neurologic problems, hematologic disturbances, or fetal growth restriction. The study by Beasley et al.¹⁵ did not provide the definition of preeclampsia.

Overall, the methodological quality of the included trials was good (Figure 2). Six studies were considered to be free of important biases.^{16–19,21,22} Three studies were stopped early: Chappel et al.¹⁴ because a planned interim analysis showed a potential beneficial effect for the primary biochemical endpoint (PAI-1/PAI-2), Beasley et al.¹⁵ because of lack of funding, and Xu et al.²⁰ because concerns arose after reviewing the evidence reported in 2 previous trials^{16,17} and internal data on serious adverse events. One study¹⁵ did not report method of allocation concealment and there was insufficient information to judge the risk of selective outcome reporting.

Primary outcome

There was no significant difference in the risk of preeclampsia between women receiving supplementation with vitamins C and E versus those allocated to placebo (9.6% vs 9.6%; RR 1.00, 95% CI 0.92 to 1.09) (Figure 3). There was evidence of low statistical heterogeneity ($I^2=13\%$) among trials reporting preeclampsia and the funnel plot appeared symmetrical either visually or when tested statistically ($P=0.86$). The effect of vitamins C and E on the risk of preeclampsia did not change after sensitivity analysis limited to the six trials considered to be free of the main sources of bias (RR 1.02, 95% CI 0.93 to 1.11; $I^2=0\%$).

Vitamins C and E did not decrease the frequency of preeclampsia in either women at low/moderate risk (6.5% vs 6.0%; RR 1.08, 95% CI 0.95 to 1.23; $I^2=0\%$) or high risk (16.3% vs 17.2%; RR 0.95, 95% CI 0.85 to 1.06; $I^2=10\%$) (Table 2). In addition, supplementation with vitamins C and E did not reduce the risk of preeclampsia in women at high risk of developing such disorder, regardless of the specific risk factor present at enrollment, although there was a statistically non-significant reduction of preeclampsia among primiparous women with BMI ≥ 30 kg/m² receiving vitamins C and E (10.7% vs 14.1%; RR 0.76, 95% CI 0.55 to 1.05). There were no significant differences between the groups in the risk of severe preeclampsia, eclampsia, and HELLP syndrome.

Secondary outcomes

Table 3 shows the risk of other adverse maternal outcomes. There was a statistically significant increase in the risk of gestational hypertension among women receiving vitamins C and E, when compared to women receiving placebo (21.5% vs 19.4%; RR 1.11, 95% CI 1.05 to 1.17; $I^2=0\%$; NNT for harm 47, 95% CI 33 to 106). This increased risk was statistically significant in women at low/moderate risk (RR 1.10, 95% CI 1.04 to 1.17) and marginally significant in women at high risk (RR 1.16, 95% CI 1.00 to 1.34) of developing preeclampsia. Vitamin C and E supplementation was also associated with an increase in the

use of any antihypertensive therapy (3.5% vs 2.0%; RR 1.77, 95% CI 1.22 to 2.57; $I^2=0\%$; NNT for harm 66, 95% CI 30 to 235; two trials, 4272 women). One trial¹⁷ reported that supplementation with vitamins C and E in nulliparous women was associated with an increase in the risk of hospitalization of women because of hypertension (RR 1.54, 95% CI 1.00 to 2.39). Another trial in high risk women¹⁶ found that more women in the vitamin C and E supplementation group than in the placebo group received magnesium sulfate (RR 1.81, 95% CI, 1.13 to 2.91). The risk of abruptio placentae was significantly lower in the group of women who received vitamins C and E than among women who received placebo (0.6% vs 1.0%; RR 0.63, 95% CI 0.43 to 0.94; $I^2=0\%$; five trials, 13,075 women). The number of women needed to treat with vitamins C and E rather than with placebo to prevent 1 case of abruptio placentae is estimated to be 280 (95% CI 178 to 1742).

There was no significant difference between the vitamin and placebo groups in the risk of severe gestational hypertension, pulmonary edema, admission to the intensive care unit, and maternal death. Supplementation with vitamins C and E was associated with a significant increase in the risk of PROM (2 trials; 3070 women; 9.6% vs 5.6%; RR 1.73, 95% CI 1.34 to 2.23; $I^2=0\%$; NNT for harm 25, 95% CI 14 to 55), and a non-significant increase in the risk of PPROM (6 trials; 17,032 women; 3.5% vs 2.9%; RR 1.30, 95% CI 0.93 to 1.80; $I^2=66\%$). An examination of the substantial degree of heterogeneity among trials evaluating PPROM found that such heterogeneity was entirely explained by the trials of Roberts et al²¹ and McCance et al.²² After excluding these trials, the sensitivity analysis limited to the remaining 4 trials (6,302 women) yielded a significant and homogeneous increase in the risk of PPROM (4.6% vs 2.7%; RR 1.68, 95% CI 1.29 to 2.18; $I^2=0\%$; NNT for harm 53, 95% CI 28 to 127).

No significant differences were seen between the two groups for any of the fetal or perinatal outcomes (Table 4) although a non-significant increase was seen in the risk of stillbirth in the vitamins C and E group compared with the placebo group (1.0% vs 0.8%; RR 1.27, 95% CI 0.93 to 1.72; $I^2=10\%$).

All funnel plots showed no asymmetry, either visually or in terms of statistical significance ($P>.10$ for all, by Egger test).

COMMENT

The pooled evidence in our systematic review showed that supplementation with vitamins C and E during pregnancy does not reduce the risk of preeclampsia in women either at low/moderate or high risk for this disorder. Moreover, we found compelling evidence that vitamins C and E increase the risk of gestational hypertension. In addition, there was some evidence suggesting that vitamin C and E supplementation is associated with a decreased risk of abruptio placentae and an increased risk of PROM and use of any antihypertensive therapy. The reliability and robustness of our results are supported by: 1) the use of the most rigorous methodology for performing a systematic review of randomized controlled trials; 2) the inclusion of all the large planned trials that investigated the efficacy of vitamins C and E during pregnancy for the prevention of preeclampsia in meta-analyses; 3) the high methodological quality of the majority of trials included in the review; 4) the evidence of clinical and statistical homogeneity in the results for most of the maternal outcomes evaluated; 5) the subgroup analyses according to risk status of women at trial entry; 6) the exploration of potential sources of heterogeneity; 7) the symmetrical funnel plots suggesting that there was no evidence of either publication or related biases; and 8) the narrow confidence intervals obtained which made our results more precise.

Our study has some limitations. First, several studies did not report results of some outcome measures considered in our review. Thus, our meta-analysis may be underpowered for such

outcomes. It is possible that if these results were reported more consistently, effect sizes might be different. Second, to date, no trials have reported on the long-term consequences of exposure of mothers and their children. Finally, we could not investigate the effect of supplementation with vitamins C and E in women with biochemical evidence of increased oxidative stress due to lack of data. Specific quantitative indices of oxidative stress such as products of lipid peroxidation could be considered as entry criteria in clinical trials of vitamins C and E during pregnancy.

Antioxidants, mainly vitamins C and E, have been proposed as a potential preventive strategy on the basis of data suggesting a role of increased oxidative stress in the pathogenesis of preeclampsia. It is unclear why supplementation with vitamins C and E during pregnancy did not reduce the risk of preeclampsia. First, it is possible that although oxidative stress plays a major role in the pathophysiology of preeclampsia, it is not important in the causal pathway of the disorder. Thereby, it would be unlikely that reversing the oxidative stress would reduce the risk of preeclampsia. On the other hand, oxidative stress could be relevant to the pathogenesis of preeclampsia in only a subgroup of women, with no appreciable benefit of vitamins C and E for the entire population. Nevertheless, in our stratified analyses by risk category at trial entry, supplementation with vitamins C and E did not decrease the risk of preeclampsia in nulliparous women with a singleton pregnancy or women with previous preeclampsia, eclampsia or HELLP syndrome, chronic hypertension, renal disease, pregestational diabetes, BMI ≥ 30 kg/m² in the first pregnancy, abnormal uterine artery Doppler velocimetry, antiphospholipid syndrome or multiple pregnancy.

It has been proposed that supplementation with vitamins C and E starting in the early second trimester after placentation has occurred might be too late to affect the pathological process of the condition. However, in the study by Roberts et al.²¹ there were no significant differences between the vitamin and placebo groups in the frequency of the primary outcome (composite of pregnancy-associated hypertension and serious adverse maternal or perinatal outcomes) among women enrolled before the 13th week of pregnancy. Finally, the beneficial effect of supplementation with vitamins C and E reported initially by Chappell et al.¹⁴ could have been due to a type I statistical error because such study was not powered for preeclampsia. In addition, this small trial was stopped early after an interim analysis showed a significant decrease in the risk of both the primary outcome (PAI-1/PAI-2 ratio) and the secondary outcome (preeclampsia). Recently, Bassler et al.³⁴ reported that randomized controlled trials that are stopped early for benefit (whether or not as a result of a formal stopping rule) are associated with greater effect sizes than randomized controlled trials that continue to the end. In addition, differences in treatment effect size between truncated and non-truncated randomized controlled trials were greatest in small trials that were stopped early.

Supplementation with vitamins C and E was clearly associated with a small but significant increase in the risk of gestational hypertension. This finding was consistent with the higher use in both antihypertensive therapy and magnesium sulfate, and a marginally significant increase in antenatal hospitalization due to hypertension. However, it is possible that these results reflect a reporting bias because only two studies described the use of antihypertensive therapy and only one study reported the use of magnesium sulfate and antenatal hospitalization for hypertension. Vitamin C and E supplementation during pregnancy also appeared to be associated with a significant increased risk for PROM and a non-significant increased risk for PPRM. Nevertheless, a sensitivity analysis excluding two trials responsible for statistical heterogeneity showed that women supplemented with vitamins C and E had a 67% increased risk of PPRM. The direction of the treatment effect was consistent in the two trials reporting PROM and in four of six trials reporting PPRM.

These findings stand in contrast to the emerging evidence suggesting that oxidative stress caused by increased reactive oxygen species formation and/or antioxidant depletion may disrupt collagen and cause premature membrane rupture.^{35,36} The explanation for why supplementation with vitamins C and E increases the risk of gestational hypertension and PROM is unknown. Banerjee et al.²⁷ have hypothesized that non-antioxidant effects of exogenous vitamin E could have detrimental effects on human pregnancy. Vitamin E therapy could prevent an immunologic switch from T-helper cell 1 to T-helper cell 2 that is vital for early-to-late transition in normal pregnancies. Moreover, vitamin E could be a potential interferon-gamma mimetic that might facilitate persistent proinflammatory reactions at the fetal-maternal interface. Regardless of what causes the increase in gestational hypertension and PROM, these findings raise concern about the use of vitamins C and E during pregnancy at the doses used in the trials included in our review.

Unexpectedly, we found that supplementation with vitamins C and E during pregnancy was associated with a significant reduction (37%) in the risk of abruptio placentae. All five studies reporting on this secondary outcome showed a similar trend. Recruitment of a sufficient cohort of women to a randomized controlled trial to confirm this finding would be very difficult. Notwithstanding, this association could be of interest for the investigation of etiology and pathophysiology of abruptio placentae. In 1957, Martin et al³⁷ reported that nine out of ten cases of abruptio placentae occurred in women with low serum ascorbic acid levels during pregnancy. Moreover, Clemetson and Cafaro³⁸ reported in 1981 that women with low serum ascorbic acid levels during pregnancy (<0.4 mg/dL) had a significantly higher risk of developing abruptio placentae than women with normal levels (unadjusted RR 9.8, 95% CI, 3.5 to 27.4). Two studies by Sharma et al^{39,40} showed that serum levels of vitamins A, C and E were lower in women with abruptio placentae than in women with normal pregnancies. Finally, Ejima et al⁴¹ have found evidence that oxidative stress is involved in placental dysfunction and abruptio placentae in a model of placental dysfunction associated with inflammation in pregnant mice. Thus, the role of vitamins C and E in the etiology and pathogenesis of abruptio placentae deserves further research.

It has been suggested that supplementation with vitamins C and E during pregnancy could reduce the risk of preeclampsia in women with a low baseline antioxidant status. In the study by McCance et al,²² women with a low antioxidant status at baseline (plasma ascorbate <10 µmol/L or serum α-tocopherol 5 µmol/mmol cholesterol) assigned to receive vitamins C and E had a reduced risk of preeclampsia compared with similar women assigned to receive placebo, although the numbers were small and the differences did not achieve statistical significance. No other trials reported their results according to baseline antioxidant status. In the study by Villar et al,¹⁹ vitamin C and E supplementation did not prevent preeclampsia in high-risk women presumed to have low antioxidant status on the basis of data from previous studies in the participating centers. In a small randomized controlled trial, supplementation with antioxidants (vitamins A, B6, B12, C, and E, folic acid, N-acetylcysteine, copper, zinc, manganese, iron, calcium, and selenium) was associated with a reduction in the rate of preeclampsia from 29% to 7% (RR 0.24, 95% CI 0.06 to 1.01) in 60 women with low antioxidant status (superoxidedismutase <1102 U/g Hb or <164 U/mL) at 8 to 12 weeks of gestation.⁴² A completed but not yet published randomized controlled trial involving 360 women with low antioxidant status at 10–12 weeks gestation assessed whether supplementation with vitamins C and E is beneficial in such women.⁴³

Three previous meta-analyses examined the effect of vitamin C and E supplementation during pregnancy on the risk of preeclampsia.^{44–46} The authors of these reviews concluded that supplementation with vitamins C and E does not prevent the development of preeclampsia in agreement with results of our meta-analysis. However, the last 4 trials

published during 2009 and 2010,^{19–22} with a total of 14,781 women, were not included in any of these previous reviews. In addition, one of these meta-analyses included quasi-randomized and non randomized trials.⁴⁶

In conclusion, the results of this review do not support routine supplementation with vitamins C and E during pregnancy to prevent preeclampsia or other adverse maternal or perinatal outcomes in women at both low/moderate and high risk for such disorder. Further research is required to determine the long term effects of supplementation with vitamins C and E during pregnancy for both women and children.

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Figure 1.
Flow of study identification

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Beazley 2005	+	?	+	+	?	-
Chappell 1999	+	+	+	+	+	-
McCance 2010	+	+	+	+	+	+
Poston 2006	+	+	+	+	+	+
Roberts 2010	+	+	+	+	+	+
Rumbold 2006	+	+	+	+	+	+
Spinnato 2007	+	+	+	+	+	+
Villar 2009	+	+	+	+	+	+
Xu 2010	+	+	+	+	+	-

Yes (low risk of bias)
 Unclear
 No (high risk of bias)

Figure 2.
Methodological quality summary: risk of biases for each included study

Figure 3.
 Effect of vitamins C and E on preeclampsia

TABLE 1

Characteristics of studies included in the systematic review

Study, year	Location	Inclusion/exclusion criteria	No of women/fetuses or infants		Daily doses of vitamins	Gestational age at trial entry (weeks)
			Vitamins C and E group	Placebo group		
Chappell, ¹⁴ 1999	United Kingdom	Inclusion: abnormal Doppler velocimetry in either uterine artery at 18–22 weeks' gestation or a history in the preceding pregnancy of preeclampsia necessitating delivery before 37 weeks gestation, eclampsia or HELLP syndrome. Exclusion: heparin or warfarin treatment, abnormal fetal-anomaly scan, or multiple pregnancy.	141/141	142/142	Vitamin C: 1000 mg Vitamin E: 400 IU	16–22
Bezzley, ¹⁵ 2005	United States	Inclusion: History of prior preeclampsia, chronic hypertension, insulin-requiring diabetes mellitus, or multiple gestation. Exclusion: not reported.	52/52	48/48	Vitamin C: 1000 mg Vitamin E: 400 IU	14–20
Poston, ¹⁶ 2006	United Kingdom	Inclusion: preeclampsia in the pregnancy preceding the index pregnancy requiring delivery before 37 weeks' gestation, diagnosis of eclampsia or HELLP syndrome in any previous pregnancy, essential hypertension requiring medication, diabetes requiring insulin or oral hypoglycemic therapy before the pregnancy, antiphospholipid syndrome, chronic renal disease, multiple pregnancy, abnormal uterine artery Doppler velocimetry, or primiparity with body mass index $\geq 30 \text{ kg/m}^2$ at first antenatal visit. Exclusion: women unable or unwilling to give written informed consent, being treated with heparin or taking vitamin supplements that contained doses of vitamin C of 200 mg or more or vitamin E of 40 IU or more daily.	1196/1393	1199/1391	Vitamin C: 1000 mg Vitamin E: 400 IU	14–21
Rumbold, ¹⁷ 2006	Australia	Inclusion: nulliparous women with a singleton pregnancy. Exclusion: multiple pregnancy, potentially lethal fetal anomaly, thrombophilia, chronic renal failure, antihypertensive therapy, or specific contraindications to vitamin C or E therapy such as hemochromatosis or anticoagulant therapy.	935/935	942/942	Vitamin C: 1000 mg Vitamin E: 400 IU	14–22
Spinnato, ¹⁸ 2007	Brazil	Inclusion: chronic hypertension or a prior history of preeclampsia. Exclusion: planned delivery elsewhere, multifetal gestation, allergy to vitamin C or vitamin E, requirement for aspirin or anticoagulant medication, 24-hour urinary protein $\geq 300 \text{ mg}$ or more, pre-pregnancy diabetes mellitus, known fetal anomaly incompatible with life, or prior participation in the study.	355/356	352/352	Vitamin C: 1000 mg Vitamin E: 400 IU	12–19
Villar, ¹⁹ 2009	India, Peru, South Africa, and Viet Nam	Inclusion: chronic hypertension, renal disease, preeclampsia-eclampsia in the pregnancy preceding the index pregnancy, requiring delivery before 37 weeks' gestation, HELLP syndrome in any previous pregnancy, pregestational diabetes, primiparity with body mass index $\geq 30 \text{ kg/m}^2$, history of medically indicated preterm delivery, abnormal uterine artery Doppler velocimetry or antiphospholipid syndrome. Exclusion: women unable to give informed consent, being treated with warfarin or taking vitamin supplements that contained doses of vitamin C of 200 mg or more or vitamin E of 50 IU or more daily.	681/753	674/762	Vitamin C: 1000 mg Vitamin E: 400 IU	14–22
Xu, ²⁰ 2010	Canada and Mexico	Inclusion: women between 12–18 weeks' gestation which were stratified by the presence or absence of risk factors for preeclampsia (history of preeclampsia, chronic hypertension, multiple pregnancy, or diabetes).	1167/1243	1196/1293	Vitamin C: 1000 mg	12–18

Study, year	Location	Inclusion/exclusion criteria	No of women/fetuses or infants		Daily doses of vitamins	Gestational age at trial entry (weeks)
			Vitamins C and E group	Placebo group		
Roberts, ²¹ 2010	Unites States	Inclusion: women who regularly consumed supplements >200 mg/day for vitamin C and/or >50 IU/day for vitamin E, taking warfarin, with known fetal malformations, with history of medical complications including epilepsy, cancer, and endocrine, renal, collagen vascular, liver, heart, serious pulmonary, and hematologic diseases, with repeated spontaneous abortion, and those who used an illicit drug during the current pregnancy. Exclusion: nulliparous women with a singleton pregnancy. Exclusion: Blood pressure 135/85 mm Hg, proteinuria, history or current use of anti-hypertensive medication or diuretics, use of vitamins C > 150 mg and/or E > 75 IU per day, pregestational diabetes, current pregnancy being a result of in vitro fertilization, regular use of platelet active drugs or non-steroidal anti-inflammatory drugs, known fetal abnormalities, documented uterine bleeding within a week of screening, uterine malformations, history of medical complications, illicit drug or alcohol abuse during current pregnancy, intent to deliver elsewhere, or participating in another interventional study.	4993/4993	4976/4976	Vitamin E: 400 IU Vitamin C: 1000 mg Vitamin E: 400 IU	9–16
McCance, ²² 2010	United Kingdom	Inclusion: women with a singleton pregnancy, type 1 diabetes preceding pregnancy, and age 16 years or older. Exclusion: women who did not give consent, enrolled in another research study, being treated with warfarin, known to misuse drugs, and taking vitamin supplements containing 500 mg or more vitamin C or 200 IU or more vitamin E daily.	379/379	382/382	Vitamin C: 1000 mg Vitamin E: 400 IU	8–22

HELLP, hemolysis, elevated liver enzymes, and low platelets

TABLE 2

Effect of vitamins C and E on preeclampsia

Outcome	Population	No of trials	No. of events/Total No.		Relative risk (95% CI)	I ² (%)
			Vitamins C and E	Placebo		
Preeclampsia	All women	9 ^{14,22}	954/9899	949/9911	1.00 (0.92 – 1.09)	13
	Women at low/moderate risk	3 ^{17,20,21}	442/6757	409/6768	1.08 (0.95 – 1.23)	0
	Women at high risk	7 ^{14,16,18–20,22}	512/3142	540/3143	0.95 (0.85 – 1.06)	10
	Women with previous preeclampsia	4 ^{16,18–20}	266/806	254/793	1.01 (0.90 – 1.14)	0
	Women with chronic hypertension	5 ^{14,16,18–20}	201/871	197/853	1.00 (0.84 – 1.19)	35
	Women with diabetes	5 ^{15,16,19,20,22}	83/609	99/602	0.84 (0.65 – 1.10)	0
	Women with multiple pregnancy	3 ^{16,19,20}	50/339	47/380	1.21 (0.84 – 1.73)	0
	Women with BMI ≥ 30 kg/m ² in first pregnancy	2 ^{16,19}	56/522	74/526	0.76 (0.55 – 1.05)	37
	Women with abnormal uterine artery Doppler velocimetry	2 ^{16,19}	10/79	6/64	0.95 (0.40 – 2.29)	NA
	Women with chronic renal disease	2 ^{16,19}	6/39	9/36	0.70 (0.29 – 1.64)	NA
Severe preeclampsia	Women with antiphospholipid syndrome	1 ¹⁶	2/29	4/23	0.40 (0.08 – 1.98)	NA
	All women	6 ^{14,16,19–21}	257/8226	258/8239	1.00 (0.84 – 1.18)	0
	Eclampsia	5 ^{16,18,19,21,22}	17/7604	10/7583	1.66 (0.77 – 3.57)	0
	HELLP syndrome	5 ^{16,18,19,21,22}	23/7604	21/7583	1.09 (0.60 – 1.97)	36

CI, confidence interval

NA, not applicable

BMI, body mass index

HELLP, hemolysis, elevated liver enzymes, and low platelets

TABLE 3

Effect of vitamins C and E on other adverse maternal outcomes

Outcome	No of trials	No. of events/Total No.		Relative risk (95% CI)	I ² (%)
		Vitamins C and E	Placebo		
Gestational hypertension	7 ^{14,16,17,19-22}	2043/9492	1842/9511	1.11 (1.05 – 1.17)	0
Severe gestational hypertension	6 ^{14,16,17,19-21}	283/9113	257/9129	1.11 (0.94–1.31)	0
Use of any antihypertensive therapy	2 ^{16,17}	74/2131	42/2141	1.77 (1.22 – 2.57)	0
Antenatal hospitalization for hypertension	1 ¹⁷	49/935	32/942	1.54 (1.00 – 2.39)	NA
Use of magnesium sulfate	1 ¹⁶	47/1196	26/1199	1.81 (1.13–2.91)	NA
Abruptio placentae	5 ^{14,18,19,21,22}	40/6549	63/6526	0.63 (0.43 – 0.94)	0
Pulmonary edema	4 ^{16,17,21,22}	8/7503	15/7499	0.53 (0.23 – 1.26)	0
Admission to intensive care unit	3 ^{16,19,20}	23/3044	32/3069	0.73 (0.43 – 1.24)	0
Maternal death	6 ^{16,18-22}	2/8771	4/8779	0.60 (0.14 – 2.51)	0
Premature rupture of membranes	2 ^{18,20}	146/1522	86/1548	1.73 (1.34 – 2.23)	0
Preterm premature rupture of membranes	6 ¹⁷⁻²²	298/8510	250/8522	1.30 (0.93 – 1.80)	66

CI, confidence interval

NA, not applicable

TABLE 4

Effect of vitamins C and E on adverse fetal and perinatal outcomes

Outcome	No. of events/Total No.			Relative risk (95% CI)	I ² (%)
	No of trials	Vitamins C and E	Placebo		
Low birth weight	6 ^{15,16,18,19,21,22}	1098/7926	1106/7911	0.99 (0.92 – 1.07)	41
Small for gestational age	9 ^{14,22}	1037/10245	1061/10288	0.99 (0.91 – 1.06)	27
Preterm birth <37 weeks	9 ^{14,22}	1606/10245	1612/10288	1.00 (0.94 – 1.06)	19
Fetal death	6 ^{16-18,20-22}	97/9299	98/9336	0.99 (0.75 – 1.31)	24
Stillbirth	6 ^{16-18,20-22}	92/9299	73/9336	1.27 (0.93 – 1.72)	10
Neonatal death	6 ^{16-18,20-22}	42/9299	55/9336	0.76 (0.51 – 1.14)	0
Perinatal mortality	8 ^{14,16-22}	191/10193	198/10240	0.97 (0.80 – 1.18)	0
Congenital malformation	3 ^{19,20,22}	68/2375	59/2437	1.19 (0.83 – 1.69)	25
Admission to NICU	4 ^{16,19,21,22}	1118/7518	1097/7511	1.02 (0.95 – 1.10)	16
Respiratory distress syndrome	6 ^{16-18,20-22}	576/9299	592/9336	0.99 (0.87 – 1.12)	26
Necrotizing enterocolitis	6 ^{16-18,20-22}	23/9299	32/9336	0.65 (0.22 – 1.94)	54
Neonatal sepsis	3 ²⁰⁻²²	49/6615	43/6651	1.10 (0.48 – 2.52)	68
Retinopathy of prematurity	5 ^{16,18,20-22}	33/8364	27/8394	1.22 (0.74 – 2.02)	0
Intraventricular hemorrhage (any grade)	2 ^{16,20}	21/2636	24/2684	0.89 (0.49–1.60)	45
Grade III/IV intraventricular hemorrhage	4 ^{16-18,21}	11/7677	14/7661	0.79 (0.36 – 1.72)	0
Periventricular leukomalacia	3 ^{17,18,20}	1/2534	1/2587	1.02 (0.14 – 7.24)	0
Neonatal seizures	3 ^{18,20,22}	10/1978	5/2009	2.01 (0.69 – 5.88)	0
Use of surfactant	2 ^{16,17}	66/2328	57/2333	0.64 (0.11 – 3.68)	80
Mechanical ventilation	5 ^{16-18,20,22}	178/4306	173/4360	1.04 (0.84 – 1.29)	27
Chronic lung disease	2 ^{17,22}	3/1314	10/1324	0.30 (0.08 – 1.09)	0

CI, confidence interval

NICU, neonatal intensive care unit