Vitamin C And Vitamin E Supplementation In Pregnant Women At Risk For Pre Eclampsia: A Randomized Controlled Trial.

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Citation

Abstract
Evidence suggests that antioxidant supplementation reduces risk of preeclampsia. Our aim was to investigate the potential benefit of antioxidants in women with risk factors of preeclampsia. A total of 285 women identified at risk of preeclampsia were administered vitamin C 1000 mg, vitamin E 200mg / placebo from 12 weeks of pregnancy till delivery in intention to treat. The patients were randomly assigned to drug groups. The incidence of preeclampsia, intrauterine growth retardation, and caesarean between placebo and vitamin group were compared and were found to be same. But preterm birth reduced in statistically significant number in vitamin group (OR = 0.28, CI = 0.21 - 0.99, p = 0.01).

INTRODUCTION
Pre-eclampsia is a multisystem disorder characterized by hypertension and Proteinuria occurring in second half of the pregnancy. This condition is best described as a pregnancy specific syndrome of reduced organ perfusion secondary to vasoconstriction and endothelial activation.¹ The exact incidence of pre-eclampsia is unknown, but about 5% pregnant women develop pregnancy induced hypertension. Out of this 35% will have one major complication.² Eclampsia is responsible for nearly 12% of all maternal mortalities in world² and 1.8% mortality in UK. As per National Family Health Survey 2005-2006 International institute of population Sciences Mumbai (2007), 10.3% women will have convulsions. Because of the seriousness of the condition studies to find means of preventing and treating pre-eclampsia are very important. Hypertension along with hemorrhage and sepsis forms the deadly triad responsible for majority of maternal deaths. There is increasing evidence that pre-eclampsia is associated with both increased oxidative stress and reduced antioxidants defenses. Circulating levels of oxidative stress markers have been found to be elevated and that of antioxidants depressed in women with pre-eclampsia compared to women without the disorder.³, these observations on the effects of oxidative stress in pre-eclampsia have given rise to increase interest in the potential benefits of antioxidant therapy given for the prevention of hypertensive disorders of pregnancy.

Antioxidants are a diverse family of components that function to prevent overproduction of and damage caused by noxious free radicals. Examples of antioxidants include Vitamin E and C. various studies including one by Chappell et al⁴ showed that daily supplements of Vitamin C 1000mg and 400mg significantly reduced a pregnant woman's risk of developing pre-eclampsia. However, a recently published review article obtained from Cochrane Library by Nicolas P Polyzos et al.⁵ stated that there was no difference in development of pre-eclampsia between vitamin and placebo groups. Similar findings were reported by other studies.⁶,⁷ In view of conflicting findings, there is need for more studies including ours. In most of the previous studies the dose of Vitamin E given was 400mg. However, some reports including one by Yusuf et al⁸ in the literature reported adverse effects of Vitamin E 400mg and therefore it was decided to reduce its dose to 200mg for the present study.

OBJECTIVES
The aims of the study were:

Primary aim

1. To investigate whether supplementation by Vitamin C 1000mg and Vitamin E 200mg decreases the incidence of hypertensive disorders of pregnancy

Secondary aim
1. To substantiate the observation that primi Para are at more risk of preeclampsia as compared to multi-gravida.

2. To find out the difference in incidence of pre-eclampsia, small for gestational age(below 10th percentile) and Preterm or low birth weight babies(less than 2.5 kg) and Caesarean section rate between the vitamin and placebo group.

3. To make recommendations accordingly.

**HYPOTHESIS**

Pre-eclampsia is associated with both increased oxidative stress and reduced antioxidants defenses. Circulating levels of oxidative stress markers have been found to be elevated and that of antioxidants depressed in women with pre-eclampsia compared to women without the disorder. These observations on the effects of oxidative stress in pre-eclampsia have given rise to increase interest in the potential benefits of antioxidant therapy given for the prevention of hypertensive disorders of pregnancy. Antioxidants are a diverse family of components that function to prevent overproduction of and damage caused by noxious free radicals. This study is designed to test the hypothesis that treatment of pregnant women with antioxidants would alter endothelial cell injury linked to preeclampsia reducing the incidence of hypertensive disorder during pregnancy.

**METHODS**

The study was conducted in the Department of Obstetrics and Gynecology of Government Medical College Hospital, Chandigarh. The present study was prospective randomized control interventional trial conducted during the period extending from June 2006 to August 2007. A total of 285 primigravida attending antenatal clinic were enrolled/registered. The group IA was administered orally vitamin-C 1000mg and vitamin-E 200mg and was labeled as intervention group (Vitamin Group). There were 145 subjects in this group. The group IB consisting of 140 primigravida subjects was randomly selected and was given oral placebo. Hence it was labeled as placebo group. Double blinding was ensured by random allocation of study subjects and coding of drugs. Another group comprising of 100 multi-gravida women (group-II) was also registered and was labeled as low risk group, intended to be meant for substantiating the findings that multi-gravida are at low risk for development of preeclampsia. Hence a total of 385 subjects (145 of group IA, 140 of group IB and 100 of group II) were enrolled for the study. All the above women were given iron and folic acid from 12 weeks of pregnancy onwards to complete 100 doses. All the above women were followed up throughout pregnancy for any evidence of gestational hypertension or pre-eclampsia, and any evidence of intra uterine growth retardation (IUGR), incidence of preterm births and Caesarean section rates. Assessors were trained for giving interventions and evaluating outcome parameters efficiently before conducting the study. For further analysis only women satisfying following inclusion criteria were selected: agreeing to participate in the study, were primigravida with singleton pregnancy, and willing to deliver at our Institute. The exclusion criteria were women with BP > 130/85 mmHg at enrollment or already on antihypertensive treatment, with proteinuria, intent to deliver elsewhere, suffering from medical disorders like diabetes, hypothyroidism etc, known fetal malformations, or already using Vitamin C (more than 150 mg) or vitamin E (more than > 75 IU/day), or NSAID (Non steroidal anti-inflammatory drug). Statistical analysis was done by using Normal test of proportions, Chi square-test, Odds ratios along with 95% confidence interval. SPSS-12 software was used for conducting statistical analysis.

**RESULTS**

At the outset with the aim of substantiating whether primi are at higher risk for various complications like preeclampsia, preterm labor, IUGR, LSCS etc., their incidence in primi was compared with multi-gravida mother without any intervention in either group. There were 4 cases of eclampsia out of total of 100 multi gravida in contrast to 11 cases in primigravida (group IB). Since among multi-gravida (group-II) pre-eclampsia, as compared to primi-gravida (group-IB) was significantly less even without intervention, this group II - was excluded from further analysis. Out of 140 primigravida registered as group IB, 18 were lost to follow up and 16 delivered outside. Thus final analysis was for 109 subjects. Out of total 145 primi-gravida registered and intended for intervention (IA group), 16 lost to follow up and 22 delivered outside. Hence final analysis for 107 subjects was done. The patients of placebo and vitamin group were well matched economically and educationally, compared to placebo group, vitamin group has less pre-eclampsia disorder but it was not statistically significant (OR = 0.44, p = 0.12). However a chance association finding of reduced rate of preterm birth (birth weight < 2.5 kg) was observed in supplemented group (OR = 0.28, CI = 0.21 to 0.99, p = 0.01) which is statistically significant. Growth retarded babies did not show any statistically significant reduction in supplemented group as...
compared to placebo group (OR = 0.93, CI = 0.38-2.31, p = 0.82, X^2 = 0.03). Vitamin supplementation could not significantly reduce the caesarean rate (P=0.42), odds ratio corresponding to the mode of delivery was found to be 0.76. No adverse events or side effect was observed in any of the intervention group (Table 1).

**DISCUSSION**

The overall incidence of pre-eclampsia was 7.04% which is in agreement with 7.6% incidence observed by Hauth et al. Observing no significant difference in the incidence of pre-eclampsia between vitamin and placebo group by present study is in agreement with other authors. The latter group used same doses of Vitamin C but Vitamin E dose was more (i.e. 400mg) compared with 200mg used in our study. Compared with 11/107 (9.1%) incidence in placebo group, the incidence of pre-eclampsia was less; 5/109 (4.8%) in vitamin group but its incidence in multi-gravida (group-II) was also low; only 4/100 (4%) even without intervention, substantiating the finding of multi-gravida being at lower risk of pre-eclampsia. A South Australia based study also concluded that no relation of eclampsia with vitamin C or E levels exists. They, however used a reduced dose of vitamin C (158 mg) and vitamin E (6.76 mg). The study by Joseph A et al also concluded that no relationship exists even after using vitamin C (1000mg) and vitamin E (400mg). Our analysis does not support to the hypothesis that vitamin C (1000 mg) and vitamin E (200 mg) supplements given prophylactically from 12 weeks onwards leads to reduction in the rate of pre eclampsia in women, but can reduce the rate of preterm deliveries.

**CONCLUSION**

The supplementation of vitamin E and vitamin C to pregnant women at risk of preeclampsia did not alter the rate of development of preeclampsia, intrauterine growth retardation or the rate of caesarean sections in this study. Vitamin E and vitamin C supplementation did decrease the risk of preterm deliveries in the vitamin group as compared to placebo group. However, larger multicentric studies are needed to support these results.

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