



Original Research Article

INVESTIGATING ANTIOXIDANT EFFECT OF VITAMINS E, C ON THE INCIDENCE RATE OF PREECLAMPSIA AND MATERNAL AND FETAL PROGNOSIS IN PATIENTS WITH INCREASED RISK OF PREECLAMPSIAAli Ghomeishi¹ and Mahin Najafian^{2*}¹Department of Anesthesiology, and Pain Research Center, Ahwaz Jundishapur University of Medical Sciences, Ahwaz, Iran.²Department of Obstetrics & Gynecology, School of Medicine, Ahwaz Jundishapur University of Medical Sciences, Ahwaz 61357-15794, Iran.

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Abstract: Disorders of hypertension in pregnancy are a component of the triple causes related to the morbidity and mortality of mother and baby. In the investigations, the role of oxidative stress has been proven in the pathophysiology of preeclampsia and the effect of free radicals in endothelial dysfunction. Essential nutrients such as vitamins C and E are able to eliminate free radicals that lead to cellular damage. Due to the cases above, this study was conducted to investigate the antioxidant effect of vitamins E&C on the incidence of Preeclampsia in pregnant women with high risk in terms of the incidence of this disease. The present study is a clinical trial. The statistical population includes 700 at risk women in terms of preeclampsia (nulliparas women). Subjects were in the age range of 20 to more than 35 years, with insulin-dependent diabetes, multiple pregnancies, overweight, previous preeclampsia history, chronic hypertension, vascular disease, collagen disease and renal disease. Patients were divided into two groups of 350 persons including the control group that just received Iron and folic acid and treatment group that received the antioxidant (E & C) in addition to iron and folic acid, afterwards the incidence rate of preeclampsia and its intensity was investigated in the two groups. Analysis was conducted by the chi-square method. The incidence rate of preeclampsia had no significant difference in the two groups of control and treatment but the incidence severity was less in the treatment than control group ($P < 0.001$) and also weight less than 2500 grams and gestational age less than 37 weeks was more in the control than treatment group. This difference was statistically significant ($P < 0.001$). According to the above-mentioned cases, consumption of antioxidants in patients with high risk in terms of preeclampsia can decrease severity of illness, reduce and improve neonatal and maternal outcome. Therefore, the use of these antioxidants is recommended during pregnancy in patients with preeclampsia.

Key Words: Vitamins E and C, prognosis, preeclampsia, mother and fetus

INTRODUCTION

Preeclampsia and eclampsia during pregnancy period affect the health of mother and fetus. Thus preventing them is of particular importance (1). Preeclampsia when applied that after 20 weeks of pregnancy, in addition to increasing blood pressure to the rate of 140.90 mm Hg or more, Proteinuria (Protein excretion) in urine to the extent of 200 mg in 24-hour urine and/or more than +2 by dipstick in the two measurements lasts for a period of 6 hours and/or pathological edema (swelling in face or hands or > +3) as sudden weight gain (equal to or more than 0.5 kg per week).

In the absence of timely diagnosis of preeclampsia, general convulsion called Eclampsia occurs (2). Disturbances such as an increase of creatinine rate to more than 1.2 mg/dl in the absence of its previous increase, platelet count less than 100.000 per cubic millimeter, Microangiopathic hemolysis (elevation of LDH), increase in AST or ALT, persistent headache or other cerebral or visual disorders and severe epigastric pain or headache also have been reported in these patients (3,4). Disorders of hypertension occur in over 10.5% of all pregnancies and are accompanied by infection and bleeding, factors

that are a significant share in maternal mortality and morbidity (5-7). In a study conducted by Kahn *et al.*, (2006), 16% of all maternal deaths have occurred due to disorders of hypertension in developed countries (8).

In the study of Berg *et al.*, (2005), more than half of deaths related to hypertension were preventable (9). Despite extensive studies, the cause of preeclampsia remains unclear (10). Known predisposing factors including abnormal aggression of thromboplasts, immunologic factors of Vasculopathy, vascular invasive changes, nutritional factors, free radicals of oxygen, peroxidation of lipids and genetic factors and also cytokines such as tumor necrosis factor and interleukins may be associated with preeclampsia in the oxidative stress (11-13).

It has also been shown in studies that the presence of inadequate nutrition in the diet, especially in terms of protein, calcium, sodium, magnesium and vitamins A, E and C may be of predisposing factors for preeclampsia (14). In a study conducted in the past, it was stated that the plasma level of vitamin C was significantly lower in women's group with

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preeclampsia compared with women in the control group (15).

Other perilous factors include pregnancy at a pregnancy early and high age, first pregnancy, history of chronic hypertension, obesity, multiple births, history of preeclampsia in a previous pregnancy, race, ethnicity, parity and insulin-dependent diabetes (16, 17). Regardless of underlying etiology, effects of events that lead to Preeclampsia syndrome include an assortment of disorders that cause the endothelial damage associated with vascular spasm, Transudation (leakage) of plasma and the consequences of ischemic and thrombotic, and free radicals strengthen this endothelial dysfunction (18, 20).

It has also been shown in other studies that preeclampsia affects the various organs of the mother including kidney, heart and liver. HELLP syndrome is another important complication of this disease (including hemolysis, increase of hepatic enzymes and decrease of blood platelets) so this syndrome can be accompanied by the poor prognosis of pregnancy (21).

In 1916, preeclampsia was called a disease of assumptions and after almost a century, this attitude still exists and the exact cause of preeclampsia is as yet unknown. Under the assumptions raised, many attempts have been made to prevent preeclampsia including the use of aspirin with low-dose, diuretics, low-salt diet, anti-hypertensive, calcium, fish oil, antioxidants, etc. (16, 17, and 22). In some studies imbalance between lipid peroxides and antioxidants has been reported in preeclampsia, also, serum level of antioxidants (vitamins of C and E) has been reported Low in patients with preeclampsia (12, 21, 23).

Studies have shown that consumption of rich substances from vitamin C and E decreases risk of preeclampsia and eclampsia (24, 26). Vitamin C is one of the important nutrients that the mothers need to increase during pregnancy (27). According to the above cases and the importance of preeclampsia, in this study antioxidant compound leading to restoration of the endothelial damage has been used.

Different results have been reported in previous studies. Our antioxidants introduced in this survey are vitamins E and C, both of which are not contraindicated in pregnancy (15). Thus, the main objective of the present study is to investigate antioxidant effect of vitamins E and C in reducing the complications of preeclampsia in the mother and the fetus.

MATERIALS AND METHODS

This study is a clinical trial and case-control. Our statistical populations studied are pregnant women above 20 weeks that are in terms of the preeclampsia development in high risk and include the following risk factors:

Pregnancy under 20 years, pregnant of nulliparous, age over 35 years, multiple pregnancies, history of chronic hypertension, history of preeclampsia in previous pregnancy, insulin-dependent diabetes, high weight (BMI \geq 30) and history of collagen and renal vascular disease that are referred to in the medical center.

The patients then were divided into two groups; group therapy that received daily 1 gram (1000 mg) vitamin C and 400 units of vitamin E from week 18 till the end of pregnancy and of course, both groups took folic acid and iron from the beginning of the study. The control group was given only iron and folic acid and wasn't given antioxidants of C and E.

These two groups were checked during pregnancy each month up to 28 weeks, every two weeks from 28 to 36 weeks, and after this, every week. Criteria for the diagnosis of preeclampsia was considered as blood pressure greater than or equal to 140/90 and proteinuria greater than or equal to +1 or urinary excretion of 300 mg in 24 hours and patients' blood pressure during this period was checked regularly by the mercury indicator.

Every two groups in terms of the preeclampsia incidence rate (after exit of a few patients in both groups, 350 people finally remained in each group) were compared. The factors researched in the present study include gestational age, incidence of preeclampsia, severity of preeclampsia, mode of delivery, age at birth and birth weight. The results were then statistically analyzed by SPSS-16 software and using descriptive and inferential statistics. The relative and absolute frequency distribution tables, calculation of central and dispersion indices and independent t-test were used for quantitative comparison in the two treatment and control groups.

Chi-square test and Fisher's exact test were used to compare qualitative variables in order to determine significance or insignificance of the variables value between the two groups mentioned and reliability coefficient was determined $\alpha = 0.05$ and CI = % 95 in the present study.

RESULTS

Since both groups were, in terms of the incidence of preeclampsia at high risk and there were old and low age in both groups, in the treatment and control group, the mean age was respectively 28.8 ± 5.9 and 29.1 ± 6.2 that so there isn't significant difference between the two groups (Figure 1).

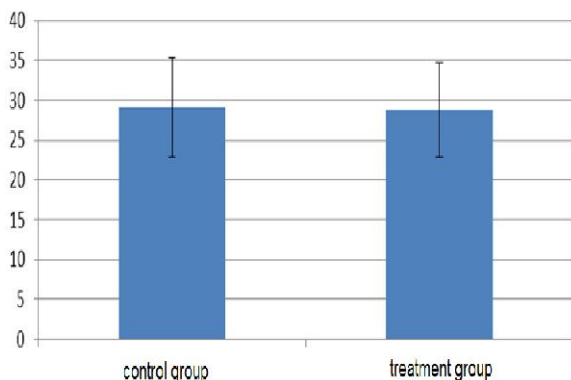


Figure 1: The mean age of the two treatment and control groups

The results show that the method of delivery (termination of pregnancy) in the two control and treatment groups has significant difference in both cesarean and vaginal delivery. The cesarean rate is significantly less in the treatment than the control group. The natural birth is also greater in the treatment than the control group (Figure 2).

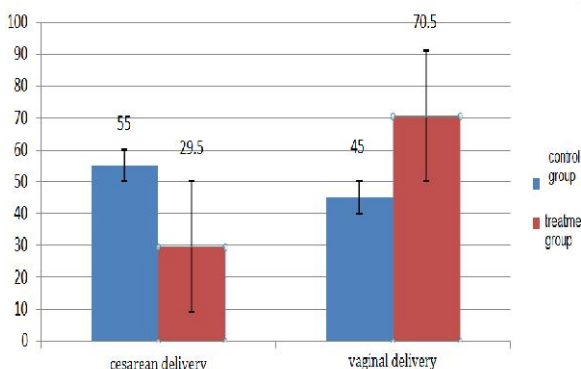


Figure 2: Mode of delivery (termination of delivery) in both treatment and control groups

In the control group in which 350 pregnant women were at the high risk of preeclampsia and were not treated with antioxidants (vitamin C, E) and received only iron and folic acid, Preeclampsia prevalence is 18.5 percent including 65 cases in which 45 and 20 cases are severe and mild, respectively. Moreover, here was no difference in terms of the preeclampsia incidence with the treatment group but in terms of the severity, the difference was significant ($p < 0.005$).

As in the control group, most cases of preeclampsia induced in the patients (45 cases) have been of severe type that in total, 69% of cases of preeclampsia were created is in this group. While the in the treatment group, the severe preeclampsia only was 14 cases, i.e., 23% vs. 69%, respectively ($p < 0.001$). Others who developed preeclampsia in the treatment group were all of the mild type, 47 cases, which is 69% (Table 1 and Table 2).

Table 1: Mean incidence rate of preeclampsia in the treatment and control groups

Complications	Treatment group		Control group		P
	number	percentage	number	percentage	
Incidence rate of preeclampsia	61	17.5	65	18.5	Ns

Table 2: Mean incidence severity of preeclampsia in the treatment and control groups

Incidence severity of disease	Treatment group		Control group		p value
	number	percentage	number	percentage	
Severe preeclampsia	14	23	45	69	$P < 0.001$
Mild preeclampsia	47	69	20	31	$P < 0.001$

Delivery less than 37 weeks is 16% and 38% ($p < 0.001$) in the treatment and control group, respectively and weight less than 2500 g is 11% and 35% ($p < 0.001$) in the treatment and control group, respectively. Data in Table 3, show that administration of antioxidants in this study to all patients in the control and treatment who have been individuals with high risk for preeclampsia, has not decreased the incidence of preeclampsia but has decreased least preterm birth and birth under 2500g and this is a significant decrease ($P < 0.001$) as well as in terms of the preeclampsia severity, it was found that in the treatment group, the incidence of severe preeclampsia is significantly lower than the control group ($P < 0.05$) (Table 3).

Table 3: Complications incidence rate between the two treatment and control groups

Complications	Treatment group		Control group		P
	number	percentage	number	percentage	
Delivery under weeks	38	16	118	38	$P < 0.001$
Weight under 2500	34	11	115	35	$P < 0.001$

DISCUSSION

In the present study, people's age-related changes with Preeclampsia in both treatment and control groups have no significant difference with each other but it was stated in the past that according to the rate of correlation, there is an inverse relationship between age and vitamin C level, so that the higher the

age, the lower the Vitamin C level (2, 28). Distribution of subjects' age in the present study can be one reason for the lack of significant difference in the average of subjects' age. As mentioned before, results represent a reduction in incidence risk of low birth weight, Preterm and reducing the risk of severe preeclampsia incidence in the group treated with tested antioxidants (vitamins C and E); however, significant difference has not been found in the total incidence of preeclampsia. Chappell *et al.*, in one study showed effective co-administration of vitamin E, C to avoid the incidence of preeclampsia in women with high risk ($P < 0.05$) and treatment with antioxidants had significantly reduced endothelial cells damages (19). It has been stated in other studies that from a total of 6082 samples studied between the use of placebo and antioxidants, 39% reduction in the risk of preeclampsia was observed (29). In Nasrollahi *et al.*'s study, reduced incidence of preeclampsia was observed in the antioxidant consumers (30). On the basis of another study that was conducted to determine the relationship between plasma vitamin C condition with preeclampsia, results showed that in terms of the amount of ascorbic acid included in the plasma, there was statistically significant difference between women with preeclampsia (whether mild or severe) and healthy pregnant women (31). Thus, the use of vitamins and antioxidants can improve Preeclampsia, which is consistent with the results of this study. Furthermore, in a study by Zhank *et al.*, that was a case-control study, it was concluded that the risk of preeclampsia in women using less than 85 mg vitamin C in their diet compared with others is 2-fold and the consumption of vegetables and rich ingredients in antioxidants decreases the risk of preeclampsia incidence (25). In a study by Aspnavt *et al.*, risk of preeclampsia in women receiving vitamin E & C was 13.8 percent and in women taking placebo, 15.6 percent, the difference was not significant (32), which agrees with the present study. In other studies that were conducted in 2000, it was stated that the basic nutrients such as vitamins C and E as a strong defensive line in the elimination of free radicals to avoid cellular damage are introduced and vascular endothelial damage as an important factor in the pathophysiology of preeclampsia was detected (15). So many studies have been conducted in this context and this case in which the concept of preeclampsia was identified by pre-oxidation lipids. It was concluded that the increase in free radicals provides background for the process of preeclampsia.

A case-control study showed that prescribed regimen of vitamin C supplement along with vitamins A and E reduces preeclampsia (15, 33). In the present study, reducing the risk of preeclampsia in the groups treated with antioxidants C and E may be due to decreasing pre-oxidation of lipids and reducing free

radicals. The results of this study also revealed that in the groups treated with antioxidants C and E, severe incidence rate of preeclampsia has declined. The rate of preterm delivery (under 37 weeks) in the treatment group is lower than the control group. Infants' weight in the treatment group is more than control group, so statistically the above results are significant. The results also represent reduction in the complications of preeclampsia in patients treated with vitamins C and E. It has been shown in the past that the combined use of vitamin E, C in women from week of 14 to 22 to the end of pregnancy reduced the risk of preeclampsia, Eclampsia and other adverse pregnancy outcomes like lightweight and small baby and perinatal deaths (34). In 1998 in Turkey, Pvrann *et al.*, by the infusion of antioxidant vitamins to Pre eclamptic placentas of people and those with a normal pregnancy with decreased level of lipid peroxide and reduced antioxidant in preeclamptic patients were faced and by measuring level of these vitamins C and E in normal pregnancy ($n = 33$), mild preeclampsia ($n = 8$) and severe preeclampsia ($n = 16$) found that the level of the antioxidant vitamins and their useful performance in patients with Preeclampsia was reduced (35). Thus, use and administration of these antioxidants is probably effective in the treatment of patients. In studies conducted in the past it was stated that the oxidative stress hypothesis in the etiology of preeclampsia has been the main reason for the focus on vitamins E and C as supplement (36). In previous studies with administration 1,000 mg of vitamin C daily in pregnant women it was shown that vitamin C and other antioxidants have the protective effect in preeclampsia (25) hence in the present study, risk of preeclampsia has also declined in the group receiving antioxidants. The amount of preeclampsia complications has dropped, probably due to the antioxidant properties of these vitamins in reducing oxygen active species and preventing lipid peroxidation. Boston *et al.*, in their study concluded that the combined administration of vitamin E, C does not decrease risk of preeclampsia but the risk of birth with low weight increases (37), which is consistent with the results of this study.

CONCLUSION

Based on the findings of this study, the use of antioxidants (vitamin E, C) does not decrease the overall incidence possibility of preeclampsia but in patients with high risk of preeclampsia, consumption of antioxidants reduces risk of severe and dangerous incidence and significantly lowers the risk of preterm birth and low birth weight. So it can be noted here that the nutritional status correction's pregnant women and it is recommended that more dairy and food sources containing calcium, vitamins C and E be consumed and increase of the proteins intake is effective to reduce the incidence of preeclampsia

among pregnant women. It is recommended that more extensive studies with a larger sample size on patients with high risk be conducted.

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