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Investigate The Effects Of Folic Acid Supplementation On Homocysteine Levels In Women With Preeclampsia

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ABSTRACT

Pre-eclampsia is a syndrome which is characterized by the increase in blood pressure above 140/90, oedema and proteinuria, and is one of the leading causes of maternal death and of complications in pregnancy that can occur in the second half of pregnancy.Approximately 20 % of pregnant women in developing countries and 5 % of pregnant women worldwide are affected, and it is the second leading cause of maternal death in developing countries, including Iran . Homocysteine (2-amino-4-mercapto-butyric acid), is a sulphur-containing amino acid without special codon and is created by an essential amino acid methionine demethylation from the diet. Homocysteine has sulphydryl group, which makes it more susceptible to other thiol oxidation and disulphide formation. Folic acid is water-soluble vitamin, and despite the need to get pregnancy to avoid disruption process of the nervous system of the fetus, NTD for antioxidant effects reduces oxidative stress, and the concentration and oxidation of homocysteine, therefore, diet and supplements during pregnancy is important.This case-control study was conducted on healthy pregnant women visiting Taleghani and Al Zahra hospitals in Tabriz, Iran, as well as on women with pre-eclampsia admitted to these two hospitals. Fifty-eight samples were selected as controls and 58 subjects were selected as cases. The blood samples were prepared with their consents. Parameter measured included homocysteine concentration in blood. In addition, a questionnaire was completed to collect information on age, gestational stage, height, weight, weight before pregnancy and folic acid (B9) intake. The results in this study are based on the inhibition of confounding variables and indicate significant differences in homocysteine status. The people, who received folic acid supplements during pregnancy were 20, and finally 60% of them were diagnosed with gestational hypertension, have been hospitalized, and 40% of them were in the control group.Elevated homocysteine levels can be considered as a factor in the etiology of preeclampsia. The type of diet and dietary antioxidants, including folic acid, in reducing homocysteine-induced oxidative stress, and improve preeclamptic women is important.

Key words: homocysteine, folic acid, pre-eclampsia

INTRODUCTION

Pre-eclampsia is a syndrome which is characterized by the increase in blood pressure above 140/90, oedema and proteinuria, and is one of the leading causes of maternal death and of complications in pregnancy that can occur in the second half of pregnancy (1)Approximately 20 % of pregnant women in developing countries and 5 % of pregnant women worldwide are affected(2), and it is the second leading cause of maternal death in developing countries, including Iran(3) (4) (5) (6) (7). Complications of preeclampsia can be a significant increase in blood pressure, although in the normal range, swelling on the face, hands, and feet in the morning is increased in weight(>450 g/week in the last trimester of pregnancy), and protein in the urine, etc. In severe cases puffiness, blurred vision, headaches, irritability, and abdominal pain are also added; and eclampsia symptoms worsened, stretch muscles, convulsions, and coma can occur(8, 9) Homocysteine (2-amino-4-mercapto-butyric acid), is a sulphur-containing amino acid without special codon and is created by an essential amino acid methionine demethylation from the diet. Homocysteine has sulphydryl group, which makes it more susceptible to other thiol oxidation and disulphide formation(10) (11) (12) (13) (14). Homocysteine is affected by the amount of protein and increased vitamins, and during exposure to oxidative stress in the body, the use of sulfur-containing amino acid, such as, cysteine and methionine increases because they are converted to homocysteine by trans-methylation and trans sulfuration pathways, i.e., one of the risk factors for cardiovascular disease (15), oxidized homocysteine produces free radicals, such as, superoxide anion (16) (17) (18). ROS (reactive oxygen species) in biological systems are constantly produced by normal metabolism in the body and are necessary for keeping biological balance through various functions. However, overproduction of these molecules and radicals cause damage to the structure, and function of the cell membrane, polyunsaturated fatty acids, thiol groups in proteins, and nucleic acids in DNA. (19) (20)Generally, oxygen radicals are produced continuously in all living organisms and the devastating effects cause cell damage and death; and their production increases in oxidative conditions. (21)Production of ROS such as anion superoxide (- • O2), hydroxyl radical (HO.), alkyl peroxide Radical (• ROO) and alcoxyl radicals (• RO) can be enzymatic and non-enzymatic. Mitochondria are the most important cell organelles for the production of radicals, especially • - O2 and H2O2 in mammals(22) (23) (24)Therefore, determination of free radicals, a marker of oxidative stress, is proportional to the condition of the organism may have an important role in homocysteine metabolism(25) (26) (27)Beside damage from free radical-induced oxidative stress conditions, the type of diet during pregnancy and vitamin supplements, such as, folic acid can act as an antioxidant Barrier(28)Since the inverse association is between tHcy and plasma-folate levels, so people who have low-plasma concentrations of vitamin are at risk of hyperhomocysteinemia(29) (30) (31). Folic acid is water-soluble vitamin, and despite the need to get pregnancy to avoid disruption process of the nervous system of the fetus, NTD for antioxidant effects reduces oxidative stress, and the concentration and oxidation of homocysteine; therefore, diet and supplements during pregnancy is important (32) (2)Generally, after receiving a rich diet in methionine, methionine demethylation pathway began. Thus, methionine transforms to the homocysteine with s-adenosyl homocysteine hydrolase, and methyltransferase enzymes and plasma concentration of homocysteine increases, because the way back to this stage of reaction is dependent on the cycle of tetrahydrofolate.
So, the importance of folic acid reduces plasma levels of homocysteine are clear. so that the 5-methyl- tetrahydrofolate of tetrahydrofolate cycle renders. Methyl group to homocysteine by demethylation of methionine and homocysteine is converted to methionine in the presence of methionine synthase (33) (34). and obtained tetrahydrofolate converts into 5-methyl tetrahydrofolate in the presence of 5–10 dimethylene tetrahydrofolate and the cycle continues (35) (36) (37)So, folic acid supplementation during pregnancy is important to prevent hyperhomocysteinemia and its complications, including stillbirth, i.e., very low birth weight, premature birth, increased risk of preeclampsia, and neural tube defects in newborns (38)The RDA for folic

acid is 600 µg/day, and it is recommended to have 400 µg/day of B-9. As a supplement and 200 µg/day of diet containing folate, including green vegetables – citrus and fortified foods, such as, bread, cereal foods fortified with folate (1) (39). The present study aims to investigate the effect of the concentration of homocysteine and folic acid supplementation on preeclampsia.

MATERIALS AND METHODS

Sample Selection

This case-control study was conducted based on conscious informed consent of Medical Ethics Committee on 116 pregnant women admitted to teaching hospitals in Tabriz (Taleghani and Al Zahra hospitals) in 2014. and was based on objective selection criteria for participation in the study: not smoking materials drugs, lack of diseases such as diabetes, heart disease and digestive disease, no history of stroke, asthma or thyroid disorders, and not taking medication. The sample included 58 patients with pre-eclampsia; the pre-eclampsia criteria were blood pressure higher than or equal to 140/90 and proteinuria higher than 300 mg per 24 hours' urine. Other questions were asked, such as age, the gestational stage, parity, height, weight before pregnancy, weight at hospitalization and folic acid intake. After getting permission from Tabriz University of Medical Sciences and introduction letters to the hospitals, the admitted women selected were informed of the study and a participation satisfaction and consent questionnaire was completed by them. To assess the condition of the samples, test for homocysteine (hcy) was performed. Fifty-eight pregnant women in the gestational stage of the second half of pregnancy who were referred to the hospital for routine tests were selected as a control group to identify confounding or interfering parameters.

Blood Samples

Full blood samples were taken over three months from two hospitals affiliated with Tabriz University of Medical Sciences. Samples and centrifuged serums between this time period and the measuring time were frozen at a temperature of -20º.

Homocysteine Measurement

The ELISA method was used to measure homocysteine levels. In this method, the separation of free decreased homocysteine to three thiols and then converted it to SAH. After removal of anti-SAH antibody, monoclonal antibody labelled with peroxidase was added, and peroxidase activity of the antioxidant enzymes glutathione peroxidase and superoxide associated with homocysteine concentration was measured using a spectrophotometer absorbed in the samples .

receiving folic acid supplements

At the time of completing the questionnaire containing personal information To evaluate the effect of folic acid on serum levels of homocysteine and preeclampsia Both the patient and control groups receiving folic acid supplements during pregnancy were examined

Statistical analysis

Statistical analysis was performed with SPSS version18.0 software. Statistically comparisons were between the control group and cases. Differences between mean values were carried out using one-way analysis of variance. Data are represented Mean ± SEM. The differences were considered significant when $*P < 0.05$.

RESULTS

The following table shows details of the two groups' average concentration parameters as measured by the method above.

Table 1: Average concentration parameter measured, including homocysteine in the two groups of controls and case

	Mean in contorol	Mean in case	Pvalue
HCY	7.458+3.667	11.12+4.511	0.005

HCY: homocysteine

As shown in the figure 1, there are significant differences in serum homocysteine concentration among the groups of women with and without pre-eclampsia, so that women with pre-eclampsia (11.12+4.511) show higher homocysteine levels than women

without pre-eclampsia (7.458+3.667) (P<0.05).

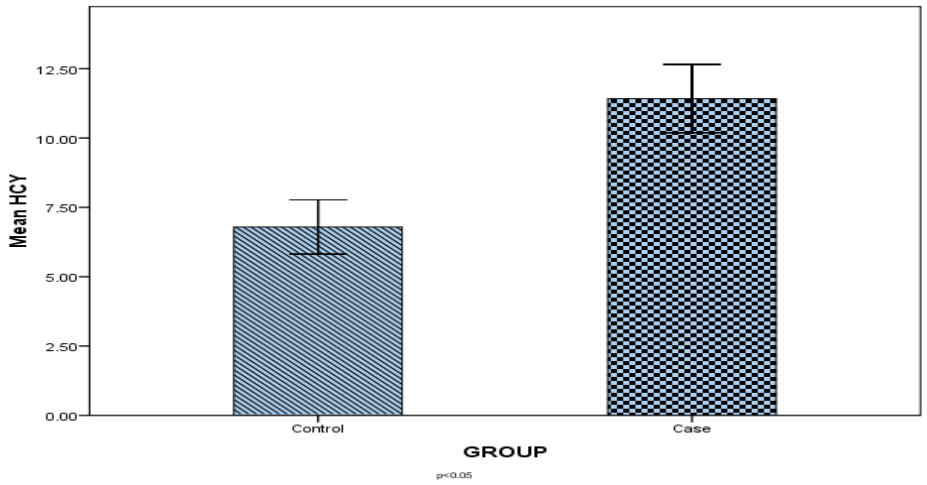

Figure 1: Mean of homocysteine concentrations between the groups of women with and without pre-eclampsia

Group Statistics

	GROUP	Mean	Std. Deviation
SBP.PR	case	146.7500	13.61782
	Control	113.8889	9.40025
DBP.PR	case	93.3621	9.29006
	Control	74.2593	6.89595

Std: standard Deviation

Table 3: The number of consumesr and those who were not used folic acid

	GROUP		
	Control	Case	Total
Not use b9	8	12	20
Use	47	49	96
Total	55	61	116

In the study of 116 people, 96 subjects received a supplement of folic acid during pregnancy Forty-nine women were patients with preeclampsia and 47 pregnant women were in the control group. The people who have not been received supplementation during pregnancy were 20. Finally, 60% of them have been diagnosed with gestational hypertension and have been hospitalized, and 40% were in the control group.

DISCUSSION

Pre-eclampsia or gestational hypertension is a multifactorial disorder that increases the sulphur-containing amino acid homocysteine. The aetiology is of general interest, since homocysteine is a marker of vascular disease(40) (41) (42) (43)Some foods contain antioxidants, including vitamins C-E and folic acid, which reduce homocysteine and pre-eclampsia the increased homocysteine level reduces the amount of antioxidant enzymes, including key elements in maintaining cellular

homeostasis and reducing oxidative damage (44) (45)found in some studies of TAS reduction in women with pre-eclampsia compared with normal pregnant women

(46)The use of proper antioxidants to enhance total antioxidant capacity and reduce vascular disease is recommended(47)Tryptophan-fortified cereals are factors that enhance TAS(48)Studies of the effects of tea and mint, and other herbal extracts, on TAS in women with pre-eclampsia show they reduce oxidative stress and increase TAS in both mother and foetus(49)Many studies on the etiology and severity of preeclampsia have associated with increased levels of homocysteine. Further, a decrease in placental folate and metabolism disorders related to folate have introduced as pathogenic factors in preeclampsia(50)Many studies on the etiology and severity of preeclampsia have associated with increased levels of homocysteine. Further, a decrease in placental folate and metabolism disorders related to folate have introduced as pathogenic factors in preeclampsia (51)Among the factors that are involved in the reduction of folic acid, methylene tetrahydrofolate reductase gene mutation,–inadequate intake of food–Sweden absorption and liver disorders can be cited(52) (53) (54)According to the recent studies during preeclampsia homocysteine-induced vascular disease increases, and the role of serum levels of folic acid is significant disagreement(55)Recognising the importance of folic acid in reducing blood pressure much research has been conducted. The study was conducted on mice and the results indicate that the intake of folic acid-rich diet low in methionine increased the ratio of albumin to creatinine and proteinuria, which is one of the symptoms of pre eclampsia(56)Generally, lack of cobalamin and folic acid deficiency increases homocysteine that is a risk factor for vascular disease, including high blood pressure(57)In this regard, a recent study results also suggest that the role of folic acid in reducing the incidence of preeclampsia.

Conclusion

Increased homocysteine leads to oxidative stress, and its effects in women with preeclampsia, and a diet rich in antioxidants, including folic acid supplements reduce the effects of oxidative stress caused by homocysteine that is considered as a predictive factor for preeclampsia.

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Conflict of Interest

The authors have declared no conflicts of interest.

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