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Effect of Folic Acid Adminsteration on Plasma Homocysteine Level in Preeclampsaia among Egyptian Population

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Abstract

Background: Hyperhomocysteinemia (HHC) appears to cause endothelial dysfunction through direct toxic and oxidative stress mechanisms. HHC was found to be seven times more common in women with history of severe preeclampsia.

Objective: The aim of this study was to determine the effect of folic acid administration on the maternal serum homocysteine level in mild and severe pre-eclamptic cases between 28 and 32 weeks of gestation.

Setting: The study was conducted on forty pre-eclamptic patients recruited from Elshatby Maternity University Hospital, Alexandria, Egypt over year 2012.

Study design: The cases were subdivided into two groups; 20 mild and 20 severe pre-eclamptic cases. Each group was subdivided into two subgroups

- Ten cases will take folic acid 5mg daily from 28 to 32 weeks.
- Ten control cases (no folic acid administration).

Results: The present study found that plasma homocysteine level was lowered after folic acid administration for both mild and severe cases. In the control group who did not receive folic acid, they had high homocysteine level .

Conclusion: Folic acid can be administrated till the second trimester of pregnancy to decrease the risk of preeclampsia.

Keywords:

Preeclampsia, Homocysteine, folic acid.

Introduction

Preeclampsia is a multi-system disorder characterized by hypertension and proteinuria in the last half of pregnancy [1,2]. Preclampsia complicates 5-7% of all pregnancies, and its life threatening manifestations make it a major cause of maternal and prenatal morbidity and mortality world wide, hence there is a critical need for strategies to predict, prevent and improve management of this disorder [3].

Some people have elevated homocysteine levels caused by a deficiency of B vitamins and folate in their diets. High homocysteine levels are also seen in people with kidney disease, low levels of thyroid hormones, psoriasis, and with certain medications (such as antiepileptic drugs and methotrexate). Patients who have the genetic variant called methylene tetrahydro folate reductase, (MTHFR) that impairs their ability to process folate are also having elevated levels of homocysteine [4].

Typically, a level less than 13μmol/L is considered normal. A level between 13 and 60μmol/L is considered moderately elevated, and a value greater than 60 to 100μmol/L is severely elevated [5]. Elevated homocysteine levels have been observed more frequently among women with certain pregnancy complications, including preeclampsia, placental abruption, recurrent pregnancy loss, and cases of intrauterine growth retardation [6]. However, medical research suggests that elevated homocysteine levels may be a consequence of these complications, rather than the cause.

The role of folic acid and homocystiene in the pathogenesis of preeclampsia has been recently described. Several studies were conducted to show an association between the level of homocysteine and preeclamptic disorders, Preeclampsia in nulliparous women with elevated homocysteine is 7.7 to 12.9 times more common than in normal controls [7-10]. The association of HHC and preeclampsia has been suggested initially by Dekker, et al. These authors demonstrated that hyperhemocystenemia was 7 times more common in women with a history of severe preeclampsia [11]. According to these authors, women with early-onset of preeclampsia showed an 18% incidence of hyperhomocysteinemia compared with a 2.5% incidence in the normal population [12].

Methodology

Patients are subdivided into two groups:

Group I: 20 patients with mild preeclampsia and **Group II:** 20 patients with severe preeclampsia. Each group will be subdivided into two subgroups where Ten cases will take folic acid in a dose of 5mg daily from 28 to 32 weeks and Ten control cases (no folic acid administration). This dose of folic acid was chosen as a treatment not prophylactic as already 400mcg was used as a routine in pregnancy for the first 16 weeks.

After approval of the medical ethics committee and signing a written informed consent all patients were subjected to: History taking and general examination, Laboratory investigation (before and after administration of folic acid): Plasma homocysteine by ELISA, Complete urine analysis to exclude urinary tract infection and to detect proteinuria, Complete blood picture, Coagulation profile, kidney function tests: serum uric acid, creatinine clearance , blood urea , serum creatinine, liver function tests: serum bilirubin, liver enzymes (ALT & AST) and Ultrasound examination before and after folic acid administration to detect the growth rate of the fetus and Umbilical artery and middle cerebral artery Doppler.

Statistics was performed using Statistical Package for Social Science (SPSS) version 17. Testing normality using Kolmogorov-Smirnov test proved that some of data sets (variables) are abnormally distributed, so median and standard error of the mean were used for descriptive statistics and non-parametric tests were used for comparison. Comparison of distribution for the categorical variable was performed using cross tabulation with Chi square test or any of the corrected Chi square as indicated. Alpha error was set to 5%.

Results

ABP (mmHg)

SBP (mmhg)	Cases			Control			P3
	On Admission	After one month	P1	On Admission	After one month	P1	
Mild							
Range	140-160	140-160		140-175	130-160		
Mean	149.50	149.00	0.425	153.50	146.00	0.050*	0.199
SD	6.43	5.16		9.73	9.66		
Severe							
Range	165-220	150-200		155-200	140-200		
Mean	181.50	175.50	0.221	177.00	160.50	0.017*	0.017*
SD	17.33	16.74		14.38	17.55		
DBP (mmhg)							
Mild							
Range	90-100	90-100		90-115	90-110		
Mean	97.50	96.00	0.212	99.50	98.50	0.397	0.219
SD	3.54	4.59		7.98	8.83		
Severe							
Range	110-170	100-120		105-120	90-115		
Mean	120.00	111.50	0.086	112.50	105.50	0.015*	0.037*
SD	18.10	5.30		5.40	7.62		
P2	0.001	0.001		0.000	0.037	-	-

Table 1: Comparison regarding blood pressure on admission and after one month of treatment

P is significant at ≤0.05.
P1 is the significant difference between admission and after one month.
P2 is the significant difference between the mild and the severe group.
P3 is the significant difference between cases and control group.

Proteinuria (gm)

Proteinuria	Cases			Control			P3
	On Admission	After one month	P1	On Admission	After one month	P1	
Mild							
Range	2-4	2-4		1-4	2-4		
Mean	2.80	3.20	0.113	2.40	2.90	0.105	0.171
SD	0.63	0.79		1.07	0.57		
Severe							
Range	3-4	2-4		2-4	2-4		
Mean	3.50	3.00	0.040	3.40	3.10	0.182	0.377
SD	0.53	0.67		0.70	0.74		
P2	0.008	0.274	-	0.012	0.253	-	-

Table 2: Comparison regarding Protienurea on admission and after one month

P is significant at ≤0.05.
P1 is the significant difference between admission and after one month.
P2 is the significant difference between the mild and the severe group.
P3 is the significant difference between cases and control group.

Homocysteine (umol/l)

Homocysteine (umol/l)	Cases			Control			P3
	On Admission	After one month	P1	On Admission	After one month	P1	
Mild							
Range	20.6-29.2	11.3-19		19.1-29.3	25.1-35.3		
Mean	23.18	14.89	0.001	24.55	29.03	0.006*	0.001*
SD	3.23	3.18		3.30	3.81		
Severe							
Range	19.4-26.1	14.4-23.5		15.4-23.7	20-32.2		
Mean	22.89	17.96	0.001	19.18	27.47	0.001*	0.001*
SD	2.55	2.74		3.27	3.50		
P2	0.415	0.016*	-	0.001*	0.177	-	-

Table 3: Comparison regarding homocysteine on admission and after one month

P is significant at ≤0.05.
P1 is the significant difference between admission and after one month.

P2 is the significant difference between the mild and the severe group.
P3 is the significant difference between cases and control group.

RI	Cases			Control			P3
	On Admission	After one month	P1	On Admission	After one month	P1	
Umbilical artery							
Mild							
Range	0.7-0.79	0.58-0.74	0.020	0.58-0.81	0.61-0.86	0.197	0.052
Mean	0.73	0.68		0.71	0.74		
SD	0.03	0.07		0.08	0.09		
Severe							
Range	0.57-0.74	0.57-0.77	0.326	0.58-0.82	0.56-6.9	0.158	0.140
Mean	0.68	0.66		0.71	1.35		
SD	0.07	0.09		0.09	1.95		
P2	0.018	0.295	–	0.479	0.169	–	–
Middle cerebral artery							
Mild							
Range	0.7-0.84	0.7-0.82	0.107	0.61-0.8	0.6-0.88	0.446	0.407
Mean	0.79	0.76		0.76	0.76		
SD	0.05	0.04		0.06	0.10		
Severe							
Range	0.74-0.81	0.73-0.78	0.137	0.7-0.9	0.7-0.82	0.016	0.034
Mean	0.77	0.76		0.79	0.73		
SD	0.03	0.02		0.08	0.05		
P2	0.122	0.321	-	0.156	0.196	-	-

Table 4: Comparison regarding resistance index (RI) on admission and after one month for umbilical and middle cerebral arteries.

P is significant at ≤0.05.
P1 is the significant difference between admission and after one month.
P2 is the significant difference between the mild and the severe group.
P3 is the significant difference between cases and control group.

Discussion

Preeclampsia is a pregnancy specific disorder characterized by vasospasm and endothelial dysfunction, and complicates 7-10 % of all gestations with serious fetomaternal morbidity and mortality [13].

Homocysteine is an intermediate amino acid in the methionine metabolism, which does not take place in the structure of proteins. It is eliminated from the body via conversion into 1- cystathione by a reaction catalyzed by vitamin B6, and two methionine catalyzed by vitamin B12 and folic acid. Homocysteine is found in low concentrations in all tissues under normal conditions where as accumulates in tissues and plasma if those catalytic vitamins are depleted. Hyperhomocysteinemia is an independent risk factor for cardiovascular diseases and common obstetric problems. Preeclampsia patients also tend to have higher plasma homocysteine levels [14-16].

Serum concentrations of homocysteine decrease during normotensive pregnancy parallel to the physiologic fall of albumin concentration and folic acid supplementation, but increases in preeclampsia like some other pregnancy complications [17-19].

In the present study, regarding blood pressure, there were statistical significant differences between mild and severe groups; severe group had values statistically higher than mild group before and after folic acid administration. Regarding mild group, there was no statistical significant differences between cases and control after one month, regarding severe group, there was statistical significant differences between cases and control after one month, cases group have values statistically higher than control group after one month of treatment. Patients with severe preeclampsia were on strict follow up and antihypertensive medications with termination of pregnancy once deterioration occurred in mother or fetus.

The present study showed that the elevated homocysteine level is directly correlated with key features of pre-eclampsia and its levels were higher in severe than mild preeclampsia. So, high maternal homocysteine levels seem to be a risk factor but not the cause of preeclampsia. In fact our study suggests the measurement of serum homocysteine in all pregnant women as a part of routine antenatal care especially those with high risk of developing preeclampsia.

Sayyah, et al., found that, there was no significant difference between the pre-eclampsia group that received 5 mg/day folic acid and control group regarding the mean arterial pressure [20].

In the current study as regard cases, before folic acid administration cases have values statistically higher than after folic acid administration. As regard mild control, they had values statistically higher on admission than after one month. On the other hand, control group after one month have values statistically higher than cases after one month. As regard severe group. As regard severe control, the values after one month were statistically higher than on admission. On the other hand, control group after one month have values statistically higher than cases after one month. When compared between mild and severe groups, regarding cases group, after folic acid administration severe group had values statistically higher than mild group, while regarding control group, mild control on admission, had values statistically higher than severe control.
The present study agreed with Leeda, et al. also the present study agreed with Van Pampus, et al. who demonstrated that hyperhomocysteinemia was seven times more common in women with history of severe preeclampsia [21,22]. Dekker, et al. in another study Powers, et al. they found a significant difference in the serum levels of homocysteine between preeclamptic patients and controls (9.0 vs. 7.0 mol/l) [23,24]. More recent studies have found a positive association between hyperhomocysteinemia in preeclamptic patients and endothelial dysfunction [25-28].

As regards Charles, et al. the effect of folic acid taken throughout the pregnancy is unclear, and folic acid supplementation commenced after the first trimester of pregnancy confers any benefit, and supports the recommendation that periconceptual folate supplements should not be continued throughout the pregnancy [29].

Murphy, et al. They found that the homocysteine concentration at delivery in mothers not supplemented with folic acid was essentially similar to that measured before conception. The concentrations of both maternal and fetal homocysteine were lowered by folic acid supplementation [30]. Finally, maternal homocysteine at preconception, at 8 weeks, and at birth was

inversely related to birth weight.

The present study disagreed with Fernández, et al. who showed that, the increase of plasma homocysteine in pregnant women, who later develop preeclampsia/eclampsia and its pathogenic role in toxemia of pregnancy, is still controversial [31].

Steegers-Theunissen, et al. in their study to assess associations between vitamin-dependent homocysteine metabolism and vascular-related pregnancy complications by considering interval between delivery and postpartum investigation and maternal age [32]. They found that hyperhomocysteinemia was associated with an approximately 2 to 3-fold increased risk for pregnancy-induced hypertension, abruptio placentae, and intrauterine growth restriction. Cobalamin deficiency was associated with HELLP syndrome, abruption placentae, intrauterine growth restriction, and intrauterine fetal death.

Regarding the Doppler indices, systolic/diastolic ratio (S/D ratio) and resistance index (RI) for both the umbilical and middle cerebral arteries. Also they are in agreement with Kwon, et al. [33].

Recommendations:

The current study determined that homocysteine level could be lowered by folic administration till 28 -32 weeks of gestation in pre-eclamptic patients. Thereby, we recommend the routine clinical practice to prescribe folic acid at a dose of 5 mg/day for pregnant women, in the second and third trimesters in addition to the first trimester to decrease the incidence of developing pre-eclampsia especially in high risk patients. Further studies and Meta-analysis are still needed to support these results.

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