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Original Research Article

The role of maternal serum homocysteine level in early onset preeclampsia for prediction of severity of disease

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ABSTRACT

Background: This study was conducted to observe the relationship between high serum homocysteine levels and preeclampsia with severe features among preeclamptic pregnant women of 20-34 weeks of gestation.
Method: This study was a hospital based a prospective cohort study and was conducted in Department of Obstetrics and Gynaecology in Dhaka Medical College. A total of 110 preeclamptic pregnant women of 20-34 weeks of gestational age were taken and data were collected after taking an informed written consent. After diagnosis of preeclampsia, I gave them some investigations like CBC, SGPT, S. Creatinine and S. Homocysteine. The patients were divided into two groups that is normal homocysteine level (Group-I) and elevated/high homocysteine level (Group-II) and then the patients were followed up by me at 2 to 4 weekly interval or more frequent if needed.
Result: Among 110 preeclamptic women, mean age of the them was 27.2±6.84 (SD) years and gestational age was 28.0±2.58 (SD) weeks when patients developed preeclampsia without severe features. Majority were nullipara (51.8%) and overweight (54.5%). The mean BMI of the preeclamptic women were 28.2±3.46 kg/m^2. The median (IQR) Homocysteine level was 11.4 (6.7-16.8) µmol/l and Hyperhomocysteinemia was reported in 31.8% of pregnant women. A cut-off value of homocysteine level ≥15.3 µmol/l showed sensitivity, specificity, NPV, PPV and accuracy 91.3%, 83.9%, 60%, 97.3% and 85.4%, respectively to correctly predict preeclampsia with severe features. Homocysteine level was significantly associated with preeclampsia with severe features ($p<0.05$) and was higher in severe preeclamptic women (91.3%). The homocysteine level was higher in patients with severe features, median-18.3 (17.6-19.4) than without severe features median 9.14 (6.68-13.5). Women with Hyperhomocysteinemia had also greater fetal complications, FGR 20%, oligohydramnios 22.9%). The relative risk ratio of development of preeclampsia with severe features was 22.5, among the preeclamptic women having S. homocysteine level ≥15.3 µmol/l**.**
Conclusion: The study shows that increased maternal serum homocysteine level at 20-34 weeks gestation in preeclampsia without severe features pregnant lady is a predictor of subsequent development of preeclampsia with severe features.

Keywords: Maternal serum, Homocysteine level, Preeclampsia

INTRODUCTION

Preeclampsia is a pregnancy specific syndrome recognized from antiquity as a leading cause of maternal and perinatal mortality. This age long disease of hypertension in pregnancy has been still a mystery in terms of etiopathogenesis.[1] It also forms the top cause of mortality in our country. This makes it one of the most researchable topics in the field of medicine and obstetrics. Preeclampsia is a disorder of pregnancy associated with new onset

hypertension, which occurs most often after 20 weeks of gestation and frequently near term. Although accompanied by new onset of proteinuria, hypertension and other signs or symptoms of preeclampsia may present in some women in the absence of proteinuria. This obstetric complication causes preterm delivery, intrauterine growth restriction, maternal and fetal morbidity and mortality.[2,3]

Hypertension is the most common medical risk factor in pregnancy. The worldwide incidence of pre-eclampsia is 2-7% of all pregnancies.[4] As per the world health report, maternal mortality due to preeclampsia and its complications during pregnancy and puerperium is around 12%.[5] In developing countries, hypertension accounts for 17% of direct obstetric deaths. Mortality rate of preeclampsia in the developing and developed countries varies, it has been recorded that approximately eight hundred women die from pregnancy and child birth related complication around the world every day.[5]

Though the exact cause of preeclampsia is still undecided, endothelial dysfunction with associated intense vasospasm has been implicated in its causation. Among bio humoral parameters, Homocysteine has recently been considered a possible remarkable cause of vascular damage. Hyperhomocysteinemia is considered as a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis. Recently homocysteine (HCY), a sulphur containing amino acid has been implicated as a missing link in causation of preeclampsia.[6]

Current hypothesis states that increased levels of Homocysteine promote oxidative stress which might damage the vascular endothelium of the developing placenta thereby increasing contractile response due to production of pro-coagulants vasoconstrictor.[7] Further, Homocysteine levels is known to increase with increasing severity of preeclampsia. Homocysteine is an amino acid which is essential for growth of cells and tissues in the human body.[8,9]

It is eliminated from the body via conversion to cystathionine by a reaction catalysed by vitamin B6 and to methionine catalysed by vitamin B12 and folic acid. Folic acid supplementation resulted in higher serum red blood cell folate and lower Homocysteine levels. Studies have reported inconsistent associations between maternal Homocysteine, measured at different time points in pregnancy and placenta mediated complications.[10] Preeclampsia is a dynamic process. Early onset preeclampsia without severe features rapidly progress to preeclampsia with severe features. So once patient develops preeclampsia, needs intense follow up and monitoring for early detection of severity.

Ideally these preeclamptic patients need hospitalization and careful monitoring, which is not always cost effective. So, measurement of Homocysteine can help prediction and categorization of patient who need careful monitoring and hospitalization. The purpose of this study was to investigate whether elevated maternal plasma homocysteine concentrations in the preeclamptic patients who were at 20-34 weeks of gestation was associated with an increased risk of severity of disease. Early onset preeclampsia often associated with many more complications such as fetal growth restriction, preterm birth, placental abruption, HELLP syndrome, eclampsia, cardiovascular disease, multiple organ damage.

Moreover, Homocysteine lowering therapies in the form of folic acid and B6 have benefited patients suffering from pre- eclampsia and eclampsia as seen in previous studies.[11] So, it may be helpful to conduct the study to explore the use of vitamins which is essential for homocysteine metabolism for prevention of preeclampsia with severe features.

METHODS

Study design

Prospective observational cohort Study.

Place of study

Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital, Dhaka.

Study period

The study duration was from January 2022 to December 2022.

Study population

Preeclamptic women without severe features at 20-34 weeks of gestation attending Fetomaternal Medicine OPD and General Obstetrics and Gynaecology OPD of Dhaka Medical College Hospital and also admitted patients in FMMU who meet up the inclusion criteria.

Sample size

The Calculated number of sample size was 100, extra 10% was taken for compensation of anticipated loss of cases during follow up. So, total sample size was 110.

Inclusion criteria

Diagnosed case of early onset preeclampsia with singleton pregnancy at 20-34 weeks of gestation. Patients who were agreed to participate in study.

Exclusion criteria

Pregnant women with DM, chronic HTN, renal or liver diseases, autoimmune diseases like SLE, APAs, H/O repeated pregnancy loss, multiple pregnancy, late onset preeclampsia.

Study procedure

Preeclamptic women who were at 20-34 weeks of gestation attending the outpatient department of DMCH for routine ANC and who fulfilled the mentioned selection criteria was selected by purposive convenient sampling. The purpose and procedure of the study was discussed with them individually. After obtaining informed written consent the women were interviewed by the researcher for the purpose of collection of data. Data regarding demographic profile, medical and family history (history of chronic hypertension, diabetes mellitus, rheumatoid arthritis, autoimmune disease, and CKD) was recorded. Obstetric history regarding gravida, parity, past obstetric history was also documented. Then a complete physical examination of the subjects was carried out by the researcher.

Furthermore, the blood pressure was taken with an appropriate procedure and proteinuria was measured by doing urinary protein creatinine ratio (PCR) test. Gestational age was confirmed by recoding CRL in early USG. Blood was collected to measure Homocysteine (HCY) level. 5 ml of fasting blood sample was collected in a plain vacutainer from preeclamptic subjects, samples were centrifuged at 3000× g to separate serum and was stored at -20℃ in an ultra-freezer until analysis and then Serum HCY was measured by ELISA method and recorded. The laboratory of Biochemistry and Molecular Biology Dept. of BSMMU used automated analyzer Atellica, Siemens Germany machine for Homocysteine analysis. Then patients were divided into two groups that is a normal HCY level (Group-I) and elevated/high HCY level (Group-II).

The participants were followed up at each visit both clinically and biochemically to assess preeclampsia with severe features. The patients were assessed clinically (measuring blood pressure, epigastric pain, headache, oliguria, sleep disturbance, blurring of vision). Every visit she was evaluated by performing Complete blood count, SGPT, S. Creatinine.Fetal complications (FGR, Oligohydromnios) were assessed by antenatal USG during followed up. The patients were followed up 2-3 weekly depending upon maternal and fetal conditions and frequent if needed. The proportion of the patient who developed hyperhomocysteinemia and preeclampsia with severe features were noted and then the association between high HCY & development of preeclampsia with severe features was assessed.

Statistical analysis

Data was processed and analyzed with the help of computer program SPSS (Statistical package for social sciences) version 24. Quantitative data was expressed as mean and standard deviation. Qualitative data was expressed as frequency and percentages. Comparisons were done by chi-square ($\chi 2$) test for categorical variable and independent student t-test for continuous variable where necessary. A probability p value of <0.05 was considered statistically significant. Area under ROC (receiver operator curve) used to find the predictive values of HCY for preeclampsia with severe features. Negative predictive value was calculated along with sensitivity and specificity.

RESULTS

Among 110 preeclamptic women, mean age of the them was 27.2±6.84 (SD) years and gestational age was 28.0±2.58 weeks when patients developed preeclampsia without severe features. Majority were nullipara (51.8%) and overweight (54.5%).

Table 1: Distribution of demographic and obstetric parameters according to homocysteine level among study population (n=110).

Variable	Normal HCY (group-I) n=75, N (%)	Elevated HCY (group-II) n=35, N (%)	P value*
Age (years)			
Mean ±SD	26.9±6.87	27.9±6.83	0.481**
Educational status			
Primary	35 (46.7)	12 (34.3)	0.462
Secondary	22 (29.3)	12 (34.3)	
Higher secondary and above	18 (24)	11 (31.4)	
Monthly income (in taka)			
<10000	16 (21.3)	3 (8.6)	0.121
10000-25000	57 (76)	29 (82.9)	
>25000	2 (2.7)	3 (8.6)	
Occupation			
Housewife	58 (77.3)	23 (65.7)	
Student	11 (14.7)	9 (25.7)	0.359
Service holder	6 (8)	3 (8.6)	
Parity			
Nullipara	46 (61.3)	11 (31.4)	0.003

Continued.

Variable	Normal HCY (group-I) n=75, N (%)	Elevated HCY (group-II) n=35, N (%)	P value*
Multipara	29 (38.7)	24 (68.6)	
Gestational age (in weeks)			
Mean±SD	27.7±2.76	28.6±2.06	0.101**
BMI (kg/m^2)			
18.5-24.9	12 (16)	6 (17.1)	
25-29.9	44 (58.7)	16 (45.7)	0.387
≥30	19 (25.3)	13 (37.1)	

*p value obtained by chi-square test, **p value obtained by independent student t-test.

The mean BMI of the preeclamptic women were 28.2±3.46 kg/m^2 and more than half of them were overweight (54.5%). Table 1 shows that parity was significantly associated with homocysteine level (p=0.003), 68.6% of women with elevated homocysteine level were multipara. The difference of age, gestational age and BMI was statistically non-significant (p>0.05).

Table 2: Relation of clinical symptoms with homocysteine level (n=110).

Variable	Normal HCY (group I) n=75, N (%)	Elevated HCY (group II) n=35, N (%)	P value*
Headache	7 (9.3)	10 (28.6)	0.009
Sleep disturbance	5 (6.7)	6 (17.1)	0.088
Blurring of vision	1 (1.3)	2 (5.7)	0.189
Epigastric pain	3 (4)	5 (14.3)	0.053
Breathlessness	1 (1.3)	1 (2.9)	0.577

*p value obtained by chi-square test.

Table 3: Distribution of maternal parameters to assess preeclampsia with severe features (n=110).

Variable	Normal HCY (group-I) n=75, Mean±SD	Elevated HCY (group-II) n=35, Mean±SD	P value*
Blood Pressure (mmHg)			
Systolic blood pressure (SBP)	142.3±7.76	154.7±7.95	<0.001
Diastolic blood pressure (DBP)	93.2±4.97	101.4±6.81	<0.001
SGPT(U/L)	34.5±36.3	48.7 ± 59.7	0.200
Serum Creatinine (mg/dl)	0.91±0.32	0.98±0.30	0.300
Platelet count(×10^9/l)	243±329	150±132	0.109

*p value obtained by independent student t-test.

Table 4: Monitoring fetal parameters of study subjects (n=110).

Fetal monitoring	Group-I (normal HCY) n=75, n (%)	Group-II (elevated HCY) n=35, n (%)
Fetal growth retardation	4 (5.3)	7 (20)
Oligohydramnios	5 (6.7)	8 (22.9)
No complications	66 (88)	20 (57.1)

Table 5: Prediction of preeclampsia with severe features according to homocysteine level at cut off value 15.3 µmol/l and relative risk (RR) measurements.

Homocysteine level	Preeclampsia		Total	RR
	With severe features n=23	**Without severe features n=87**		
Group-II high HCY (≥15.3 µmol/l)	True positive (TP) 21	False positive (FP) 14	TP+FP 35	22.5
Group-I Normal HCY (<15.3 µmol/l)	False negative (FN) 2 TP+FN23	True negative (TN) 73 FP+TN87	FN+TN 75 110	

Table 6: Association of development of preeclampsia with severe features with serum homocysteine at cut off value 15.3 µmol/l.

Homocysteine concentration (µmol/l)	Total n=110 N (%)	Preeclampsia with severe features n=23, N (%)	Preeclampsia without severe features n=87, N (%)	P value
Group-I (Normal HCY) <15.3 µmol/l	75 (68.2)	(8.7)	73(83.9)	<0.001*
Group-II (Elevated HCY) ≥15.3 µmol/l	35 (31.8)	21 (91.3)	14 (16.1)	
Median (IQR)	11.4 (6.7-16.8)	18.3 (17.6-19.4)	9.14 (6.68-13.5)	

*P value obtained by Chi-square test.

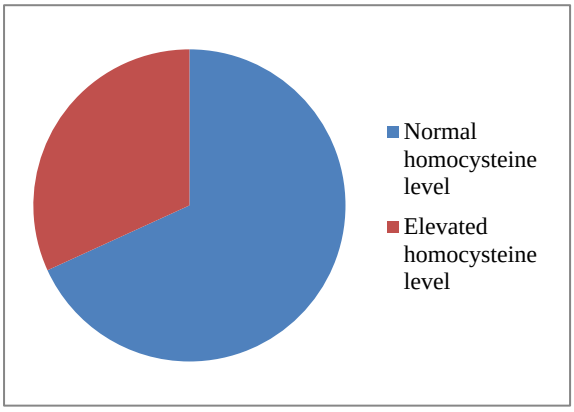

Figure 1: Distribution of homocysteine level among preeclamptic pregnant women (n=110).

The Figure 1 shows that among 110 preeclamptic pregnant women, 75 women (68.2%) had normal homocysteine level and 35 women (31.8%) had elevated homocysteine level. The total population was divided into two groups, group-I (normal homocysteine, <15µmol/l) and group-II (Elevated homocysteine,>15µmol/l). Table 2 shows that headache was significantly associated with elevated homocysteine level (p=0.009). 28.5% and 17.1% of patient with elevated HCY complained of headache and sleep disturbance respectively. 5.7%,14.3% and 2.9% of patient with elevated HCY complained of blurring of vision, epigastric pain and breathlessness respectively. Table 3 shows that the blood pressure was significantly raised in elevated homocysteine group (Group-II) (p<0.001). The mean SBP, DBP, SGPT and serum creatinine was higher whereas the mean platelet count was lower in elevated homocysteine level group compared to Group-I normal homocysteine level.

Table 4 shows that while assessing the fetal parameters, it was observed that fetal growth retardation (20%) and oligohydramnios (22.9%) was more common in preeclampsia women with elevated homocysteine level compared to group-I normal homocysteine level. Table 5 shows a cut-off value of homocysteine level ≥15.3 µmol/l showed sensitivity, specificity, NPV, PPV and accuracy 91.3%, 83.9%, 60%, 97.3% and 85.4%, respectively to correctly predict preeclmpsia with severe features. The risk of having preeclampsia with severe features in women with elevated homocysteine level was 22.5. Table 6 shows that Serum Homocysteine concentration was significantly associated with severity of preeclampsia (p<0.05). In Group–II (elevated homocysteine level) more preeclamptic women developed severe features (91.3%) and without severe features was 16.1%.

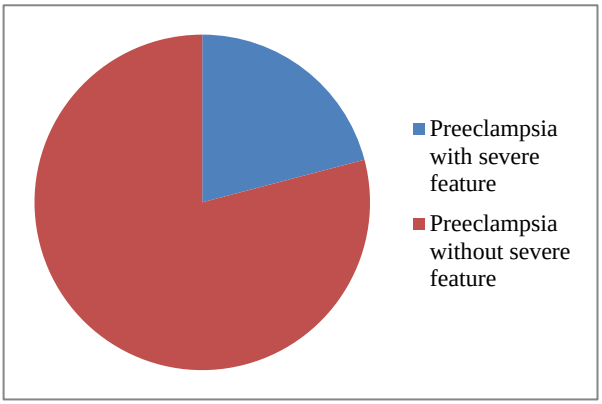

Figure 2: Distribution of preeclampsia according to its severity among pregnant women (n=110).

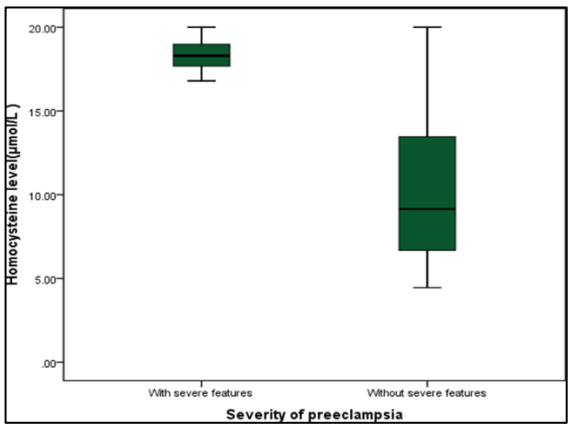

Figure 3: The level of homocysteine with severity of preeclampsia (n=110).

P value<0.001*, *P value obtained by Mann-Whitney U-test.

The Figure 2 that among 110 preeclamptic pregnant women, preeclampsia with severe features were present in 23 (20.9%) and 87 (79.1%) women had preeclampsia without severe features. The Figure 4 demonstrated that the homocysteine level was significantly associated with

severity of preeclampsia (p<0.001). The homocysteine level was higher in patients with severe features median-18.3 (17.6-19.4) than without severe features median-9.14 (6.68-13.5). Level in predicting severity of preeclampsia, with 91.3% sensitivity and 83.9% specificity. The serum homocysteine level showed an excellent area under curve (AUC: 0.919, 95%CI: 0.848 to 0.990, p<0.001) for predicting severity of preeclampsia

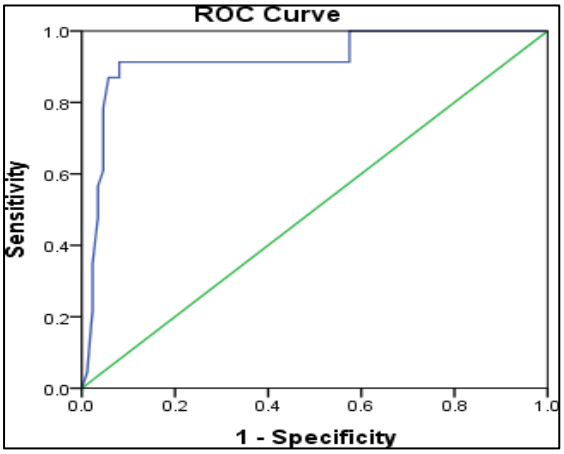

Figure 4: S. homocysteine level for prediction of preeclampsia with severe features.

DISCUSSION

Preeclampsia is a serious complication that may occur in pregnant women in second and third trimester. Preeclampsia is said to be a leading cause of maternal mortality and fetal morbidity, although the exact cause of preeclampsia is still unknown, it is known that the basic pathology is endothelial dysfunction and intense vasospasm.[12] Recently, elevated homocysteine level, a metabolite of essential amino acid methionine, has been proved to be an independent risk factor in etiology of preeclampsia.[13] This prospective cohort study demonstrated that pregnant women who developed preeclampsia with severe features had higher plasma homocysteine levels in than those women who had preeclampsia without severe features throughout pregnancy.

In addition, elevated blood pressure in early pregnancy may predict women who are at increased risk of developing preeclampsia with severe features. In this study population, the mean age of the women with preeclampsia was 27.2±6.84 years and most of them were in the age group of 26-34 years (45.5%) depicting that older age pregnant women were prone to preeclampsia. This was in agreement with the study by Javedi et al who reported severe preeclamptic women had a mean age of 27.7±5.8 and Thilaganathan B et al, reported that the mean age of the preeclamptic and healthy pregnant women to be 29.6±5.7 and 31.9±5.2 years respectively.[14,15] Among 110 preeclamptic pregnant women, preeclampsia with severe features were present in 20.9% in this study, the proportion of severe preeclampsia was much lower than the 90.0% reported in study in Lagos.[16] In the present study, the median homocysteine level of preeclamptic women was 11.4 µmol/l and elevated homocysteine level ((≥15.3) or hyperhomocysteinaemia was reported in 31.8% of the pregnant women and 91.3% of women with severe preeclampsia had hyperhomocysteinaemia. This was partially similar to the results. Were they reported 24.6% women had hyperhomocysteinaemia and 42.9% had severe preeclampsia with which was much lower compared to our study. Bergen et al reported a rate of only 22.2% in his study in contrary, maternal hyperhomocysteinaemia was reported in 50.0% of preeclamptic women in a study by Visternicean in Moldova.[17-19] This variation may be due to the geographical/racial differences and varying cut off value for elevated serum homocysteine level chosen by Visternicean (12 µmol/l) whereas the higher cut off value for the current study (>15.3µmol/l) was based on the reference range for normal homocysteine level.

The current study had shown a significant association with homocysteine level and preeclampsia with severe features (p<0.001). Women with severe features of preeclampsia had higher median homocysteine level median (IQR), 18.3(17.6-19.4) µmol/l and hyperhomocysteinaemia compared to preeclampsia without severe features median (IQR), 9.14 (6.68-13.5) µmol/l. Similarly, Dekker et al [20] revealed that serum homocysteine could be seven times greater in women with severe early onset preeclampsia compared to the normal pregnant women.

Another systematic review that assessed the hypothesized mechanism of homocysteine in preeclampsia (25 primary articles, 3,649 women), showed a positive association of serum homocysteine level with preeclamptic patients in all but one of the review articles, with a weighted mean difference of 2.50 µmol/l (95% CI 1.82–3.17, P<0.001) between preeclamptic women and healthy pregnant women.[21] In this study based on the ROC curve, the serum homocysteine levels had an excellent area under the curve (AUC:0.919) with sensitivity and specificity of the predictor variable being 91.3% and 83.9% respectively at a cut off value >15.3 µmol/l, a much lower cut-off value (>8 µmol/l) of homocysteine level was determined with an AUC of 0.975 in the study by Jahan et al with 92.7% sensitivity and 77.5% specificity.[22]

The findings in this study was also comparable to those reported by Javadi et al. who demonstrated that the mean serum homocysteine in severe preeclamptic patients were significantly higher (8.9±4.1 µmol/l) compared to controls (5.5±1.6 µmol/l, p<0.001).[14] Acilmis et al showed that maternal and fetal serum homocysteine levels to be significantly higher in severe preeclampsia group than those in mild preeclampsia and healthy controls, suggesting that level of serum homocysteine is increased with severity of preeclampsia. In contrary, Zeeman et al and Ayotunde et al reported no detectable association between maternal hyperhomocysteinaemia and preeclampsia.[23] Additionally, while observing the fetal parameters, fetal growth retardation (20%) and

oligohydramnios (22.9%) was more common in preeclampsia women with elevated homocysteine level compared to normal homocysteine level. Ghike et al reported poor fetal outcome such as more still births in hyperhomocysteinaemic preeclamptic women (6.67%) and Lindblad et al. reported that women with elevated homocysteine level had higher chances of delivery IUGR infants.[25] In the time of taming the pyramid of obstetric care, early detection of early onset preeclampsia with timely intervention is desirable in high-risk women.

Early disease identification may reduce the adverse fetal and maternal consequences of that disease. Detection of maternal serum homocysteine level is cost effective, easily available test so that easily could be used as a predictor of preeclampsia with severe features. Women at risk for preeclampsia with severe features identified in early weeks can take vitamins (vitamin B12, B6 and folic acid) and ecosprine, also they should take preconceptionally counselling. Large scale prospective study involving diverse group of population are warranted to clarify the association between Hyperhomocysteinemia and subsequent development of preeclampsia with severe features.

Like other studies the present study was also not flawless. Although optimum care has been tried by the researcher in every step of this study, some limitations still exist. Limited sample size was a major limitation. The data of the study collected from DMCH only therefore, there might be an issue of generalization of the study findings. The result of the study might not be reflecting the exact picture of the country. The present study was conducted at a very short period of time.

CONCLUSION

Although pregnancy and childbirth have never been harmless for the mother and child, preeclampsia is still an important cause of maternal and perinatal morbidity and mortality. The study concluded that homocysteine levels are significantly elevated in patients with preeclampsia and especially among preeclampsia with severe features pregnant women. Additionally, higher level of homocysteine was also associated with maternal and perinatal complications, making it an easy and less-time consuming test that can be reliable predictive marker for preeclampsia with severe features. Although it is doubtful that there will ever be a single universal predictive test for a multifactorial disease such as preeclampsia, but the use of plasma homocysteine as a screening test for severe preeclampsia requires further investigation.

Recommendations

Depending upon the study findings, recommendations are suggested, further multicenter study is recommended. Create room for the conduct of a more robust, adequately powered longitudinal research to answer some of the major reservations that remain from the present study. A larger sample size is recommended. Awareness should be developed among obstetricians towards prediction and early intervention of pregnancy complications by using different biomarkers.

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