ISSN 2347-5579

Unique Journal of Medical and Dental Sciences

Available online: www.ujconline.net

Research Article

ASSOCIATION OF SERUM HOMOCYSTEINE LEVELS WITH PREECLAMPSIA AND ITS RELATED COMPLICATIONS

Chhavi Kabra[1], Bushra Fiza[1*], Maheep Sinha[1], Swati Garg[2]

[1]Department of Biochemistry, Mahatma Gandhi Medical College & Hospital, Jaipur, India
[2]Department of Obstetrics & Gynecology, Mahatma Gandhi Medical College & Hospital, Jaipur, India

Received: 12-12-2014; Revised: 10-01-2015; Accepted: 08-02-2015

*Corresponding Author: **Bushra Fiza**
Department of Biochemistry, Mahatma Gandhi Medical College & Hospital, Jaipur (Rajathan), India, Pin: 302022

ABSTRACT

Preeclempsia is a syndrome characterized by onset of hypertension and proteinuria following the 20th week of gestation. It has significant health outcomes and increases the maternal and perinatal mortality rate. Homocysteine is a non-protein amino acid derived from cysteine. Plasma total homocysteine levels depend on many physiological, pathological and genetic determinants. Preeclampsia is said to be associated with hyperhomocystenemia. The present study was planned to assess the association of preeclampsia and its related complications with serum homocysteine levels.

60 antenatal females identified with Preeclampsia were selected for the study. Hemoglobin and serum homocysteine were estimated. The selected females were grouped on the basis of severity of preeclampsia and proteinuria and presence or absence of intra uterine growth retardation (IUGR). The values for each subgroup were indicated as mean $\pm$ SD and statistically compared by applying 't'-test. The mean homocysteine levels were observed to be higher than the normal reference range. Further, elevated homocysteine levels were observed in females with severe preeclampsia and uncontrolled proteinuria. The presence or absence of IUGR, however, did not show any significant variation. The fall in the hemoglobin levels with increased homocysteine further confirmed its association with endothelial and vascular damage.

The study concluded that hyperhomocysteinemia can serve as a significant marker for screening of preeclampsia and its related complications in the early second trimester and can be helpful in proper antenatal and fetal care and patient management.

Keywords: Homocysteine, Hyperhomocysteinemia, IUGR, Preeclampsia, Proteinuria.

INTRODUCTION

Preeclampsia is one of the most common pregnancy associated disorder and a major cause of maternal morbidity and mortality[1]. It is not a simple complication but a syndrome involving impairment of functions of multiple organs including that of liver, kidneys, lungs and the coagulatory and neural system. The pathogenesis of this disorder involves numerous factors such as oxidative stress, endothelial dysfunction, vasoconstriction, metabolic changes and inflammatory responses[2]. The etiology of preeclampsia is suggested to be abnormal placentation. The disorder is usually manifested after 20th week of gestation and the complications aggravate with the advancement of pregnancy and in the absence of proper patient management. Fetal complications in preeclampsia are directly related to gestational age and the severity of maternal disease and include increased rates of preterm delivery, intra uterine growth retardation (IUGR), placental abruption, and perinatal death[3,4].

Another clinical entity that increases the risk of perinatal morbidity and mortality is intrauterine growth retardation (IUGR). The major cause of IUGR includes maternal, fetal and placental factors. Due to common pathological features of placenta, Preeclampsia and IUGR are said to be etiologically linked together[5].

Homocysteine is a non-protein sulphydryl amino acid. It is a homologue of the amino acid cysteine derived from metabolic conversion of methionine, which is dependent on several enzymes and vitamins[6]. Homocysteine is involved in several key metabolic processes, including the methylation and sulphuration pathways. Plasma total homocysteine depends on many physiological, pathological and genetic determinants which are closely inter-related. Increased Homocysteine can lead to oxidative stress, endothelial dysfunction and haemostatic activation[7]. Previous studies have suggested that Hyperhomocysteinemia affects the blood vessel wall and brings about changes in the endothelium and smooth muscle proliferation[8-10]. Hyperhomocysteinemia has been shown to be

associated with vasculopathy, placental abruption and pregnancy hypertension[11-13].

The aim of the present study was to assess homocysteine levels in preeclampsia and its related complications including proteinuria, anemia and IUGR.

MATERIALS AND METHODS

The present study was conducted on 60 antenatal women identified with preeclampsia visiting the Obstetric outpatient department of Mahatma Gandhi hospital, Jaipur. The study protocol was approved by the institutional ethics committee. The criterion for inclusion was Blood Pressure (BP) $\geq$ 140/90 mm Hg in the second or third trimester of pregnancy in previously normotensive females.

Prior to conducting the study, relevant details regarding the chief complaints, duration of pregnancy, complete obstetric history, any chronic illness and past history were noted. A complete obstetric, general physical and systemic examination was carried out.

Routine investigations along with urine dipstick test and 24 hour urine proteins were carried out for confirmation of controlled or uncontrolled proteinuria. Serum homocysteine levels were estimated using Diazyme kit by enzyme cycling method. The cases of IUGR from the selected pre eclamptic women were diagnosed by ultrasound and clinical examination at the beginning of third trimester. The results obtained were analyzed statistically. P $\leq$ 0.05 was considered as statistically significant.

The present study was planned to assess the effect of individual pathogenic factors including proteinuria, Hemoglobin (Hb) levels and severity of preeclampsia on serum Homocysteine levels. Further the study also aimed at assessing the association of these factors with the risk of IUGR and vice versa.

RESULTS AND DISCUSSION

In the present study, mean age of the females selected was 25.7$\pm$ 5.37 years. Mean hemoglobin level was 10.10$\pm$ 1.86 gm/dl. Mean serum Homocysteine concentration was 17.91$\pm$ 9.13 µmol/L (Table 1)

Several studies have suggested and supported that preeclampsia is associated with Hyperhomocysteinemia. Most of the previous studies have compared the levels of Homocysteine in pre eclamptic women with normotensive females[14, 15, 16]. In the present study, a separate control group was not framed. However the mean serum Homocysteine levels in the present study were higher than the accepted normal reference range i.e. 5-15 µmol/L[17]. In a recent study by Patel et al, 2012[18], serum Homocysteine levels in the normotensive pregnant females was 13.45$\pm$ 4.39 µmol/L as compared to 19.96 $\pm$6.42 µmol/L in pre eclamptic females.

The females selected for the present study were grouped on the basis of severity of preeclampsia. Classification of preeclampsia was based on the guidelines of American College of Obstetrics and Gynecology as mild and severe preeclampsia[19].

Mild preeclampsia included diagnosis of gestational hypertension defined as BP $\geq$ 140/90 mm Hg on two measurements $\geq$ 6 hrs apart and proteinuria > 300mg/24 hours or $\geq$ 1+. Severe preeclampsia was defined as BP $\geq$ 160/110 mm Hg on two measurements $\geq$ 6 hrs apart and proteinuria $\geq$2+ or > 300mg/24hours by 24 hours urine examination along with any of the following: Platelets <120 K; AST > 45U/L; ALT > 60U/L or creatinine $\geq$ 1.0 mg/1dl.

Mean Hb levels showed a significant decline with severity of disease (Table 2). Previous studies have confirmed that women with mild preeclampsia generally have no symptoms or manifestations as such which became evident with the severity of preeclampsia[20, 21]. Serum Homocysteine levels showed a highly significant increase with the severity of preeclampsia. Mean serum Homocysteine level for the mild pre eclamptic group was 13.20 $\pm$3.68 µmol/L. The value obtained was very close to those reported by Patel et al, 2012 for the normotensive pregnant women. S. Homocysteine concentration in the severe preeclampsia group was as high as 23.95 $\pm$ 9.85 µmol/L. Recent studies have reported that Homocysteine levels are directly correlated with severity of preeclampsia[22, 23]. HasanZadeh M et al, 2008[24] have also suggested that women with severe preeclampsia have higher Homocysteine levels than women with mild preeclampsia or normotensive pregnant females.

The Hb level was higher (p = 0.000) in the controlled proteinuria group as compared to the uncontrolled proteinuria group. Serum Homocysteine concentration was significantly higher in the uncontrolled proteinuria group i.e.22.65 $\pm$ 10.36 µmol/L (p =0.000). Since hypertension and proteinuria are both significant markers of preeclampsia, their manifestation is expected to increase with the advancing gestational age[25]. Both hypertension and proteinuria are complications resulting from endothelial dysfunction and vascular damage[26, 27]. On the other hand, Homocysteine is considered to be an individual risk factor for arterial and peripheral vascular disease[7]. The above finding of increased serum Homocysteine concentration in conditions of hypertension and proteinuria suggest that Hyperhomocysteinemia is a significant marker of the onset of preeclampsia as well as chronic hypertension and proteinuria of pregnancy.

The period of intrauterine growth and development is the most critical period in the human life cycle. The weight and growth of the fetus are considered as the markers of the future health status in infancy, childhood and even adulthood. The etiology of IUGR is complex and involves maternal, placental or fetal causes. One or more of these factors may result in low weight of the fetus[28]. Previous studies have suggested that IUGR is associated with preeclampsia[29]. Ness and Sibai, 2006[30] suggest that the subset of women with preeclampsia and IUGR result from a maternal predisposition to endothelial dysfunction leading to shallow placental implantations. On the contrary, Villar and Carroli, 2006[5], suggest that unexplained IUGR may share similar etiology with preeclampsia, but actually the two disorders are biologically separate.

To assess the effect of Homocysteine level in cases of preeclampsia with or without IUGR, the females were grouped accordingly & mean age was calculated. No significant variation was observed in the serum Homocysteine levels in the IUGR and normal fetal growth groups. Infact, homocysteine levels were slightly lower in the IUGR group

though the change was non-significant. The above observation suggests that Homocysteine levels are higher than the normal reference range in both the conditions of preeclampsia and IUGR. However, the presence of the two together does not affect or further increase the levels of Homocysteine.

Previous studies have reported higher Homocysteine levels in women with preeclampsia[14, 31, 32] and also in conditions of IUGR[33, 34]. The above discussion suggests that preeclampsia is associated with Hyperhomocysteinemia. The Homocysteine levels are further affected by the severity of preeclampsia. The severity of preeclampsia is in turn affected by the advancing gestational age. The present study proposed that higher levels of Homocysteine can serve as markers of preeclampsia at the early onset of the disease and hence can be helpful in better antenatal care and patient management.

CONCLUSION

The study suggests that hyperhomocysteinemia is a significant marker of preeclampsia and confirms that a higher homocysteine concentration is a reliable indicator of onset of preeclampsia. Hypertension and proteinuria exhibit a strong association with hyperhomocysteinemia and hence further confirm the reliability of this marker. No significant variation was observed in the homocysteine levels in pre eclamptic females with or without IUGR. S. homocysteine level is affected by several physiological and nutritional factors and is a marker of endothelial dysfunction and vascular damage. The study therefore, recommends and proposes to further assess the correlation of this important marker with the individual risk factors of cardiovascular damage such as components of lipid profile and serum uric acid etc. especially in the early gestational age for better antenatal care and patient management.

REFERENCES

1. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet, 2005; 365: 785–799.
2. Hall DR, Odendaal HJ, Steyn DW, Grove D. Expectant management of early onset severe pre-eclampsia: maternal outcome. BJOG, 2000; 107: 1252–1257.
3. North RA, Taylor RS, Schellenberg JC. Evaluation of a definition of pre eclampsia. BJOG, 1999; 106: 767–73.
4. Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J et al. The detection, investigation and management of hypertension in pregnancy: full consensus statement. Aust. NZ. J. Obstet. Gynaecol., 2000; 40: 139–55.
5. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Preeclampsia: gestational hypertension and intrauterine growth restriction, related or independent conditions. Am. J.Obstet Gynecol., 2006; 194: 921–931.
6. Laskowska M and Oleszczuk Jan. Homocysteine in pregnancies complicated by preeclampsia with and without IUGR: a comparison with normotensive pregnant females with isolated IUGR and healthy pregnant women. OJOG, Dec 2011; 1(4): 191-196.
7. Welch GN and Loscalzo J. Homocysteine and atherothrombosis. N. Engl. J. Med., 1998; 338: 1042-1050.
8. Aubard, Y., Darodes, N. and Cantaloube, M. Hyperhomocysteinemia and pregnancy—review of our present understanding and therapeutic implications. Eu. J. Obstet. Gynecol. Reprod., 2000; 93: 57-165
9. Onalan R, Onalan G, Gunenc Z and Karabulut E. Combining 2nd trimester maternal serum homocysteine levels and uterine artery doppler for prediction of preeclampsia and isolated intrauterine growth restriction. Gynecology and Obstetrics Investigaton, 2006; 61, 142- 148.
10. Weir DG and Scott JM. Homocysteine as a risk factor for cardiovascular and related disease: Nutritional implications. Nutrition Research Reviews, 1998; 11: 311-338.
11. Budde MP, De Lange T, Dekker GA, Chan A, Nguyen AM. Risk Factors for placental abruption in a socio-economically disadvantaged region. J. Matern. Fetal Neonatal Med., 2007; 20(9): 687-693.
12. Marshal K. Intrauterine growth restriction. Curr. Opinion Obstet. Gynecol., 2002; 14: 127-135.
13. Ray JG, Laskin CA. Folic acid and homocysteine metabolic defects and risk of placental abruption, pre-eclampsia and spontaneous pregnancy loss: a systematic review. Placenta., 1999; 20: 519-529.
14. Powers RW, Evans RW, Majors AK et al. Plasma homocysteine concentration is increased in preeclampsia and associated with evidence of endothelial activation. Am. J. Obstet Gynecol., 1998; 179: 1605-1611.
15. Walker MC, Smith GN, Perkins SL, et al. Changes in homocysteine levels during normal pregnancy. Am. J. Obstet. Gynecol., 1999; 180: 660-664.
16. Hogg BB, Tamura T, Kelley E et al. Second trimester plasma homocysteine levels and pregnancy induced hypertension, preeclampsia, and intrauterine growth restriction. Am. J. Obstet. Gyn., 2000; 183: 805-809.
17. Ueland PM, Refsum H, Stabler SP et al. Total homocysteine in plasma or serum: method and clinical applications. Clin. Chem., 1993; 39: 1764-1779.
18. Patel AP, Chakrabarti C, Singh A, Patel JD, Mewada HA, Sharma SL. Effect of Homocysteine, Vitamin B12 and Folic acid during pregnancy. NHLJMS, July, 2012; 1(1): 28-32.
19. American College of Obstetrics and Gynecology Practice Bulletin 33. Diagnosis and Management of Preeclampsia and Eclampsia, January, 2002.
20. Hnat MD, Sibai BM, Caritis S, Hauth J, Lindheimer MD, Macpherson C, et al. Perinatal outcome in women with recurrent pre eclampsia compared with women who develop pre eclampsia as nulliparas. Am. J.Obstet. Gynecol., 2002; 186: 422–426.
21. Chesley LC. Diagnosis of pre-eclampsia. Obstet.Gynecol., 1985; 65: 423–425.

22. Singh U, Gupta HP, Singh RK, Shukla M, Singh R, Mehrotra SS. A study of changes in homocysteine levels during normal pregnancy and pre-eclampsia. J. Ind. Med Assoc., 2008; 106: 503-505.
23. Khosrowbeygi A, Lorzadeh N, Ahmadvand H, Shiravand H. Homocysteine and its association with lipid peroxidation and leptin in preeclampsia. Int. J. Biol. Chem., 2011; 5: 184-192.
24. Hasanzadeh M, Ayatollahi H, Farzadnia M, Ayati S, Khoob MK. Elevated plasma total homocysteine in preeclampsia. Saudi Med. J., 2008; 29: 875-878.
25. Powers RW, Evans RW, Ness RB, Crombleholme WR, Roberts JM. Homocysteine and cellular fibronectin are increased in preeclampsia, not in transient hypertension of pregnancy. Hypertension & Pregnancy., 2011; 20: 69–77.
26. Kanani PM, Sinkey CA, Browning RL, Allaman M, Knapp HR, Haynes WG. Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocysteinemia in humans. Circulation, 1999; 100: 1161-1168.
27. Mignini LE, Latte PM, Villar J, Kilby MD, Carrolli G, Khan KS. Mapping the theories of preeclampsia: the role of homocysteine. Obstet. Gynecol., 2005; 105: 411-425.
28. Bernstein PS, Divon MY. Etiologies of fetal growth restriction. Clin. Obstet. Gynecol., 1997; 40: 723–729.
29. Srinivas SK, Morrison AC, Andrela CM, Elovitz MA. Allelic variations in angiogenic pathway genes are associated with preeclampsia. Am. J. Obstet. Gynecol., 2010; 202(5): 445.e1–445.e11.
30. Ness RB and Sibai BM. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. Am. J. Obstet. Gynecol., 2006; 195: 40–49.
31. Dekker AG, DeVries JIP, Doelitzsch PM et al. Underlying disorders associated with severe early onset preeclampsia. Am. J. Obstet Gynecol., 1995; 173: 1042–1048.
32. Rajkovic A, Catalano PM, Malinow MR. Elevated homocyst(e)ine levels with preeclampsia. Obstet. Gynecol., 1997; 90: 168–171.
33. De Vries JI, Dekker JA, Huijgens PC, Jakobs C, Blomberg BM, Van Geijn HP. Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies. Br. J. ObstetGynaecol., 1997; 104: 1248–1254.
34. Vollset SE, Refsum H, Irgens LM, Emblem BM, Tverdal A, Gjessing HK, Monsen AL, Ueland PM. Plasma total homocysteine, pregnancy complications and adverse pregnancy outcomes: the Hordaland homocysteine study. Am. J Clin. Nutr., 2000; 71 : 962-968.

Table 1: Mean levels in the pre eclamptic females

n= 60	Mean ± SD
Age (years)	25.7 ± 5.37
Hemoglobin (gm/dl)	10.10 ± 1.86
S. Homocysteine (µmol/L)	17.91 ± 9.13

Table 2: Serum Homocysteine and Hemoglobin levels in the different subgroups based on complications of Preeclampsia

Groups	No. of cases (n)	Hemoglobin (gm/dl)	S. Hcysteine (µmol/L)
Mild PE	30	11.13 + 1.42	13.20 + 3.68
Severe PE	30	9.08 + 1.69	23.95 + 9.85
P-value		**0.000**	**0.000**
Controlled proteinuria	29	10.93 ± 1.56	14.22 ± 4.79
Uncontrolled proteinuria	31	9.33 ± 1.80	22.65 ± 10.38
P-value		**0.000**	**0.000**
IUGR -ve	39	9.76 + 1.79	19.50 + 9.38
IUGR +ve	21	10.74 + 1.87	16.86 + 8.68
P-value		**0.050**	**NS**

P-value as obtained on applying t-test

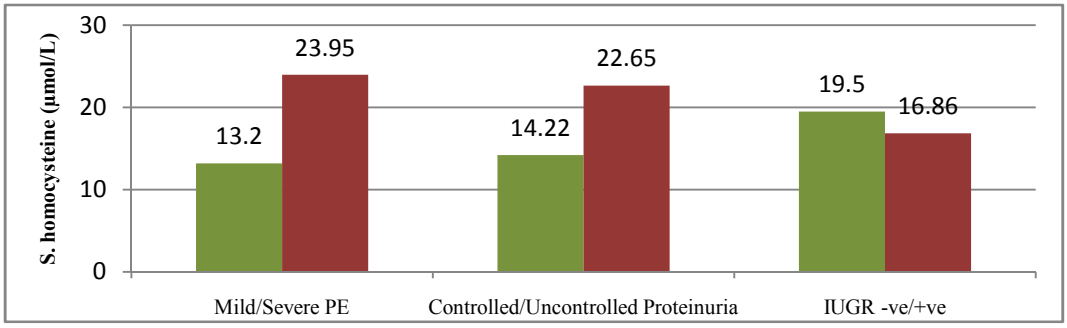

Figure 1: S. Homocysteine levels in different subgroups based on complications of Preeclampsia

Source of support: Nil, Conflict of interest: None Declared