Original Research Article

Study of correlation of serum homocysteine level with adverse pregnancy outcome

Vishal Chaudhari[1], Shubhangi Mande[2], Dhananjay Bhale[3*]

{[1]Sr. Resident, [2]Associate Professor, Department of OBGY} {[3]Professor and HOD, Department of Biochemistry}
MGM MC Aurangabad, Maharashtra, INDIA.
Email: dr.bhale@gmail.com

Abstract

Homocysteine, an essential amino acid required for the growth of cells and tissues in the human body also has an implication in the various vascular diseases when elevated. Many adverse pregnancy complications like recurrent pregnancy loss (RPL), IUGR, abruptio placentae, preeclampsia and eclampsia are associated with disturbances in the hemostatic balance and placental vasculature. During pregnancy hyperhomocysteinemia, can cause damage to the vascular system that support the placental function, and this damage might leads to miscarriage and other adverse pregnancy outcome. In our study we correlated serum homocysteine level with adverse pregnancy outcomes. We found that number of preterm deliveries in case group were significantly more and there is strong association between pregnancy complications and adverse fetal outcome. 64% women in case group had raised homocysteine levels, out of which 52% had homocysteine between 16-50mmol and 12% had homocysteine >50mmol. The rise in homocysteine levels was statistically significant in cases of preeclampsia, eclampsia and abruption. Hence, high level of homocysteine may be considered a precocious marker of vascular damage and may denote a higher risk of pregnancy complication.

Key Words: Homocysteine, high risk pregnancy, preeclampsia, abruption.

[*]**Address for Correspondence:**
Dr. Dhananjay Bhale, Professor and HOD, Department of Biochemistry, MGM MC Aurangabad, Maharashtra, INDIA.
Email: dr.bhale@gmail.com
Received Date: 27/04/2018 Revised Date: 23/05/2018 Accepted Date: 19/06/2018
DOI: https://doi.org/10.26611/1012638

Access this article online

Quick Response Code:

Website: www.medpulse.in

Accessed Date: 28 June 2018

INTRODUCTION

Homocysteine is a sulfur containing amino acid primarily derived from demethylation of dietary methionine, which is abundant in proteins of animal origin. It is an essential amino acid required for the growth of cells and tissues in the human body. Elevated circulating homocysteine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive vascular disorder[1]. Homocysteine is either converted back to methionine by remethylation or further metabolized to cysteine via the trans-sulfuration pathway. Remethylation primarily occurs when a methyl group is transferred from methyltetrahydrofolate (MTHF), the active form of the folic acid, by the methyltransferase enzyme requiring cobalamin (vitamin B12) as a necessary cofactor. A secondary remethylation pathway which is primarily active in liver and kidney cells uses trimethylglycine (betaine) as the methyl donor. The trans-sulfuration pathway requires two enzymatic reactions, both of which require the cofactor pyridoxal-5-phosphate, the active form of vitamin B6[2]. Homocysteine is also metabolized to the cyclic thioester Homocysteine-thiolactone which is a reactive intermediate. The Homocysteine-thiolactone pathway becomes predominant when remethylation or transsulfuration reactions are impaired by genetic alteration of enzymes involved in homocysteine metabolism, such as cystathionine b-synthase (CBS), methionine synthase (MS), or methylenetetrahydrofolatere-ductase (MTHFR) or by inadequate supply of folate, vitamin B-12 or vitamin B-6.

How to cite this article: Vishal Chaudhari, Shubhangi Mande, Dhananjay Bhale. Study of correlation of serum homocysteine level with adverse pregnancy outcome. *MedPulse – International Journal of Gynaecology.* June 2018; 6(3): 78-82.
http://medpulse.in/Gynacology/index.php

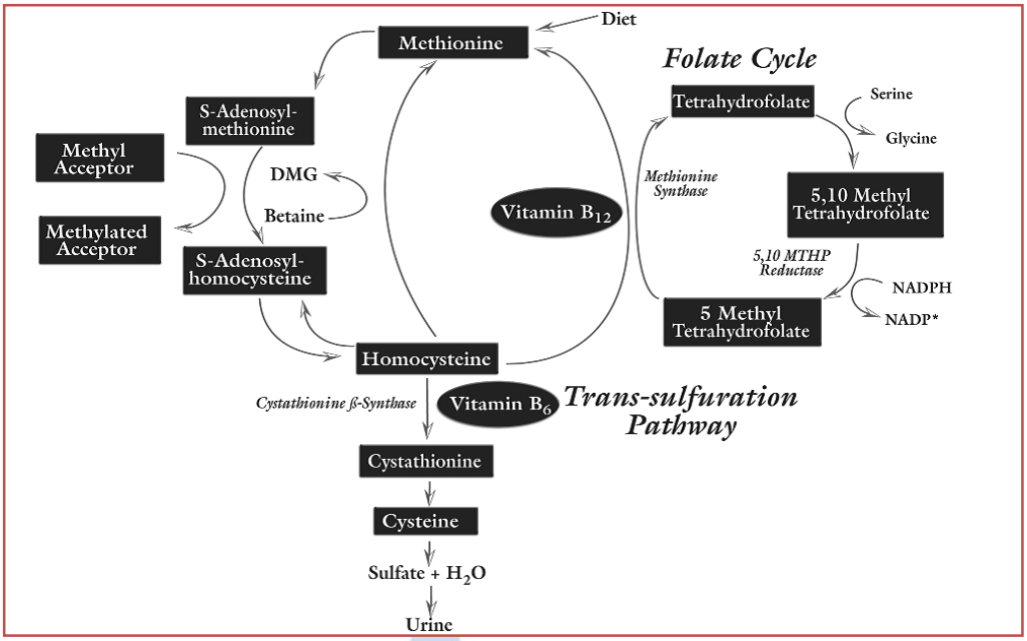

Figure 1: Metabolism of homocysteine

The process of human conception is extremely complicated and there are several factors involved in establishment and maintenance of pregnancy, placental circulation being one of them. There is a delicate balance between the coagulation system and the fibrinolytic system, which is maximally challenged at the site of implantation and subsequent development of placenta. Abnormality of placental vasculature and disturbances in hemostasis lead to inadequate fetal circulation. It has been suggested that adverse pregnancy complications like recurrent pregnancy loss (RPL), IUGR, abruptio placentae, preeclampsia and eclampsia are associated with disturbances in the hemostatic balance and placental vasculature. It has also been suggested that thrombophilias like hyperhomocysteinemia augment the relative hypercoagulable state of pregnancy. Preeclampsia and eclampsia are pregnancy specific disorder characterized by vasospasm and endothelial dysfunction, and complicates 7-10% of all gestations with serious feto-maternal morbidity and mortality. Etiology of preeclampsia is still obscured but one of the most favored hypotheses is the endothelial dysfunction secondary to the peroxidation of membrane lipids[3]. Decreased antioxidant activity and increased lipid peroxides was shown clearly in preeclamptics[4]. Hyperhomocysteinemia is an independent risk factor for cardio vascular diseases and common obstetric problems[5]. Damage to endothelial layer lining the blood vessel wall is thought to play an important role in the pathophysiology of preeclampsia.. Homocysteine is responsible for endothelial cell damage leading to proatherogenic effects, thromboembolic effects, hypoperfusion of placenta, and over production of free radicals.[6-7] During pregnancy hyperhomocysteinemia, can cause damage to the vascular system that support the placental function, and this damage might leads to miscarriage and other adverse pregnancy outcome. Hyperhomocystenemia has been suggested to augment hypercoagulable state of pregnancy[8-9], and thrombosis in maternal and fetal circulations, this considered as important mechanism of disease during pregnancy[10], it leads to abnormality of placental vasculature and disturbances in homeostasis and inadequate fetal circulation and linked with pregnancy outcome like recurrent pregnancy loss, preeclampsia, preterm labor, abruptio placenta, IUGR.[11] Several studies have indicated that homocysteine concentration increases during preeclampsia and eclampsia. But there are a few reports concerning homocysteine levels in various vascular damage related pregnancy outcome. In this study our aim is to find out correlation of serum homocysteine level with those adverse pregnancy outcomes

MATERIALS AND METHODS

This study was done in M.G.M. Medical College and Hospital, Aurangabad from September 2014- September 2016. This study included 100 women, who were divided into two groups. Case and control group. Case group consist of 50 women with severe preeclampsia, eclampsia, abruption IUGR, IUD and abortion. Control group included 50 normotensive women who had no medical complication. This is a Prospective Observational Case-Control study

The inclusion criteria of this study: Case Group- we included 50 women with major vascular damage related pregnancy complication. Patient with

- Severe Preeclampsia
- Eclampsia
- Abruption
- IUGR
- IUD
- Abortion

Control Group- 50 normotensive women without any medical complication were included.

The exclusion criteria of case group in this study

- Diabetes mellitus
- Chronic hypertension
- Preexisting renal disorder
- Preexisting liver disorder
- Immunovasculitis

Detailed examination and conventional lab investigations were carried out; from each woman 3ml of venous blood was collected in a plain bulb with strict aseptic precaution. The serum was used for serological evaluation for Homocysteine. It is measured by using Fluroscence Polarization Immunoassay method in AxSym system. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD. The chi-square test was used to determine whether there was a significant difference between the expected frequencies and the observed frequencies in one or more categories. *P*- values were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

Homocysteine level of 50 women with vascular damage related pregnancy outcome (case group) were correlated with 50 women without any pregnancy complication (control group). Both group were comparable to each other as far as there area, education, antenatal care and parity was concerned. Other factors like maternal age, gestational age, BMI, fetal birth weight and Hb% were concerned both groups were again comparable to each other except gestational age and fetal birth weight which was less in case group with mean gestational age 28.71±6.43 and mean fetal birth weight 1.64±0.94. Number of preterm deliveries in case group were significantly more (58%). Many women needed early termination in view of pregnancy complications. Many women in case group underwent in preterm labour spontaneously. From comparison of fetal outcome in case and control group it is evident that there is strong association between pregnancy complications and adverse fetal outcome. Adverse fetal outcome in the form of NICU admission (30%), FSB (10%) and MSB (42%) were observed. 64% women in case group had raised homocysteine levels, out of which 52% had homocysteine between 16-50mmol and 12% had homocysteine >50mmol. 16% women in control group were having raised homocysteine level between 16-50mmol, though no fetal or maternal complication observed in any of those women. The comparison of homocysteine levels in control and preeclampsia group shows raised homocysteine level in 59.1% women with preeclampsia which is statistically significant with $p<0.0001$ and raised homocysteine level in 71.4% patients with eclampsia. Hyperhomocysteinemia is associated with pre-eclampsia as well as eclampsia, but in eclampsia the severity of homocysteine elevation is more compared to that in pre-eclampsia. Raised homocysteine levels in 81.8% of women with Abruption, which is more as compared to control group (14%). Raised homocysteine levels are observed in 66.7% of women with IUD. Difference between both groups was statistically significant ($p<0.0001$). The serum level of homocysteine for patient with abortion involved in this study was 36.7 µmol/l.

Table 1: Demographic comparison of case and control group

Demographic Parameters		Case Group		Control Group		Chi-square value	P-value
		No	%	No	%		
Area	Rural	34	68%	32	64%		P=0.673
	Urban	16	32%	18	36%	0.178	NS
Religion	Hindu	36	72%	47	94%		P=0.003
	Muslim	14	28%	3	6%	8.58	S
Education	Illiterate	2	4%	0	-		
	Up to higher secondary	35	70%	39	78%	2.38	P=0.304
	Graduation andabove	13	26%	11	22%		NS
Booked	Booked	25	50.0%	31	62.0%		P=0.227
	Unbooked	25	50.0%	19	38.0%	1.46	NS
Parity	Primigravida	25	50.0%	24	48.0%	0.012	P=0.841
	Multigravida	25	50.0%	26	52.0%		NS

Table 2: Comparison of other factors in of case and control group

Factors	Case Group	Control Group	t-value	P-value
Maternal age	24.62±3.92	23.54±3.11	1.54	P=0.131 NS
Gestational age	28.71±6.43	38.9±4.92	10.9	P<0.00001 S
BMI	24.98±3.04	25.54±2.56	2.12	P=0.174 NS
Fetal birth weight	1.64±0.94	2.87±0.89	5.34	P=0.001 S
Hb%	11.51±1.94	11.72±2.32	2.02	P=0.261 NS

Table 3: Gestational age in case and control Group

Gestational age	Case(n=50)		Control(n=50)		Chi square value	P-value
	No.	%	No.	%		
Pre-term	29	58%	01	2.0%	37.27	P<0.0001 S
Term	21	42%	49	98%		
Total	**50**	**100%**	**50**	**100%**		

Table 4: Fetal outcome in case and control group

	Case(n=50)		Control(n=50)		Chi-square value	p-value
	No.	%	No.	%		
Baby with mother	09	18.0%	49	98.0%	67.5	P<0.0001 S
Adverse Fetal Outcome	41	82%	01	2.0%		

Table 5: Comparison of Grade of hyperhomocysteinemia in case and control group

Grades	Case(n=50)	Control (n=50)	Chi-square value	p-value
Normal(5-15mmol)	18(36%)	42(84%)	25.01	P<0.0001 S
Mildly Raised (16-50mmol)	26(52%)	8(16%)		
Severely Raised (>50mmol)	6 (12%)	00		

Table 6: Comparison of homocysteine levels in various cases

	Homocysteine level Normal	Homocysteine level Raised	Chi-square value	p-value
Sever preeclampsia (n=22)	09 (40.9%)	13 (59.1%)	13.70	P<0.0001 S
Eclampsia (n=7)	02 (28.5%)	5 (71.4%)	10.74	P<0.0001 S
Abruption (n=11)	02 (18.2%)	09 (81.8%)	19.4	P<0.0001 S
IUD(n=22)	07 (33.3%)	14 (66.7%)	18.67	P<0.0001 S
RPL (n=1)	00	1 (100%)	4.76	P=0.026 S

DISCUSSION

The remethylation of homocysteine into amino acid methionine is blocked by a lack of folate, which result in hyperhomocysteinemia. Hence elevated plasma homocysteine concentration is a sensitive marker of folate status. Lack of exercise and other characteristics of the cardiovascular disease risk profile, including blood pressure and total cholesterol, were important determinants of the homocysteine concentration. Plasma homocysteine concentration reduces in normal pregnancy, probably due to increased plasma volume and associated hemodilution, increased glomerular filtration rate, hormonal changes associated with pregnancy and increase uptake of homocysteine by fetus.

- Low level of homocysteine are present in normal pregnancy
- High level of homocysteine may be considered a precocious marker of vascular damage may denote a higher risk of pregnancy complication like preeclampsia, eclampsia, abruption, abortion and IUD.
- Early detection of the risk may allow for improvement of the pregnancy outcome by

increasing patient's surveillance or by initiating a therapeutic intervention.

- It is an easy and less time consuming test that can be reliably be considered as the predictive marker for various pregnancy complications.
- More studies are needed to elucidate the pathophysiology of hyperhomocysteinemia in above mentioned adverse pregnancy outcomes.

REFERENCES

1. Refsum, H., Ueland, P.M., Nygard, O. andVollest, S.E. Homocysteine and cardiovascular disease.Annu. Rev. Med., 49, 31-62.
2. Thomas G. Guilliams. Homocysteine – A Risk Factor for Vascular Diseases: Guidelines for the Clinical Practice. The Journal of American Neutraceutical Association Winter 2004; Vol.7, No.1:10-24
3. Dekker GA[1], Sibai BM. Etiology and pathogenesis of preeclampsia: current concepts. Am J Obstet Gynecol1998 Nov;179(5):1359-75.
4. Kharb S. Lipid peroxidation in pregnancy with preeclampsia and diabetes. Gynecol. Obstet. Invest. 2000; 50:113–116.
5. Hajjar KA. Homocysteine: a sulph'rous fire. J Clin Invest 2001; 107:663-664
6. Raijmakers MT[1], Zusterzeel PL, Roes EM, Steegers EA, Mulder TP, Peters WH. Oxidized and free whole blood thiols in preeclampsia. Obstet Gynecol. 2001 Feb; 97(2):272-6.
7. Powers, R.W., Majors, A.K., Ojimba, J.I., Ness, R.B., Crombleholme, W.R.and Roberts, J.M.(1998) Plasma homocysteine concentration is increased in preeclampsia and is associated with evidence of endothelial activation. Am. J. Obstet. Gynecol., 179, 1605-1611.
8. Martinelli P, Grandone E, Colaizzo D, et al. Familial thrombophilia and the occurrence of fetal growth restriction. Haematologica. 2001; 86:428-31.
9. Arias F[1], Romero R, Joist H, Kraus FT. Thrombophilia: a mechanism of disease in women with adverse pregnancy outcome and thrombotic lesions in the placenta. J Matern Fetal Med. 1998 Nov-Dec; 7(6):277-86.
10. Many A[1], Schreiber L, Rosner S, Lessing JB, Eldor A, Kupferminc MJ. Pathologic features of the placenta in women with severe pregnancy complications and thrombophilia. Obstet Gynecol. 2001 Dec; 98(6):1041-4.
11. Kiran Pandey, Preeti Dubay, Ajay Bhagoliwal, Neena Gupta, Geetika Tyagi. Hyperhomocysteinemia as a Risk Factor for IUGR. J Obstet Gynaecol India. 2012 Aug; 62(4): 406–408.

Source of Support: None Declared
Conflict of Interest: None Declared