Original Research Article

Clinical study of hyperhomocysteinemia and adverse obstetric outcome in patients with bad obstetric history at a tertiary hospital

Satyajeet Salunkhe[1*], Gouri Salunkhe[2]

[1,2]Assistant Professor, Department Gynaecology & Obstetrics, Bharati Vidyapeeth University, Sangli, Maharashtra, INDIA.
Email: satyajitsalunkhe@hotmail.com

Abstract

Background: Hyperhomocysteinemia in pregnant women has been associated with deep venous thrombosis, recurrent miscarriage, hypertensive disorders of pregnancy, abruption, IUGR, recurrent pregnancy loss, intrauterine death and prematurity. Present clinical study was aimed to study hyperhomocysteinemia and adverse obstetric outcome in patients with bad obstetric history at a tertiary hospital. **Material and Methods:** Present study prospective, observational study, conducted in pregnant women, antenatally booked at more than 20 weeks of gestation, attending antenatal clinic and delivered at our hospital were considered for this study and were followed for maternal and foetal outcomes at the termination of pregnancy. **Results:** In present study 35 cases (pregnant women with bad obstetric history) and 35 controls (low risk pregnant women with no history of any abortion) were studied. Age of pregnant women was comparable in both groups; difference was not significant statistically ($p>0.05$). Other general characteristics such as gravida status, parity status were more in cases while live births were more in controls, difference was statistically significant ($p<0.001$). Among cases 67.56 % had hyperhomocystenemia while controls had 11.43 % subjects with hyperhomocystenemia, difference was statistically highly significant ($p< 0.001$). Among cases high risk factor/ complications noted were preeclampsia (22.86 %), intrauterine growth restriction (17.14 %), abruption (8.57 %), gestational diabetes mellitus (5.71 %), HELLP syndrome (5.71 %), eclampsia (2.86 %) and acute kidney injury (2.86 %). In present study we noted a statistically significant difference in gestational age at delivery, birth weight, mean APGAR at 5 minutes, meconium passage, required resuscitation, neonate required NICU admission (%), neonates developed neonatal complications and required ventilator support between two groups. **Conclusion:** In patients with bad obstetric history as well as hyperhomocystenemia, adverse obstetric outcomes such as intra uterine growth restriction, preeclampsia and abruption are more common. Also in such patients, poor perinatal outcome are expected.

Keywords: bad obstetric history, hyperhomocystenemia, adverse obstetric outcomes preeclampsia, abruption

[*]**Address for Correspondence:**
Dr Satyajeet Vilas Salunkhe, Department Gynaecology & Obstetrics, Bharati Vidyapeeth University, Sangli, Maharashtra, INDIA.
Email: satyajitsalunkhe@hotmail.com

Received Date: 04/10/2021 Revised Date: 12/11/2021 Accepted Date: 22/12/2021

Access this article online

Quick Response Code:

Website: www.medpulse.in

DOI: https://doi.org/10.26611/10122034

INTRODUCTION

Bad obstetric history implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortion, early neonatal death, still birth, intrauterine fetal death, fetal growth restriction and congenital anomalies. [1] Recurrent pregnancy loss (RPL) is defined as three or more consecutive pregnancy loss prior to 20 weeks gestation Chromosomal anomaly of the parents, anatomical abnormality of the uterus and antiphospholipid antibody syndrome (APS) in addition to uncontrolled diabetes and hypothyroidism, have been directly contributed to RPL.[1] Homocysteine, a sulfur-containing amino acid derives from the demethylation of methionine during DNA or/and RNA methylation. Increased homocysteine levels represent a risk factor in cardiovascular disease, osteoporosis, renal failure, diabetic microangiopathy, neuropsychiatric disorders.[2] Hyperhomocysteinemia has been suggested to augment hypercoagulable state of

How to cite this article: Satyajeet Salunkhe, Gouri Salunkhe. Clinical study of hyperhomocysteinemia and adverse obstetric outcome in patients with bad obstetric history at a tertiary hospital. *MedPulse International Journal of Gynaecology.* December 2021; 20(3): 84-86. http://medpulse.in/Gynacology/index.php

pregnancy, and thrombosis in maternal and fetal circulations, this considered as important mechanism of disease during pregnancy, it lead to abnormality of placental vasculature and disturbances in homeostasis and inadequate fetal circulation and linked with adverse pregnancy outcome.[3] Hyperhomocysteinemia in pregnant women has been associated with deep venous thrombosis, recurrent miscarriage, hypertensive disorders of pregnancy, abruption, IUGR, recurrent pregnancy loss, intrauterine death and prematurity.[3,4] Present clinical study was aimed to study hyperhomocysteinemia and adverse obstetric outcome in patients with bad obstetric history at a tertiary hospital.

MATERIAL AND METHODS

Present study was conducted in Department Gynaecology And Obstetrics, Bharati Vidyapeeth University, Sangli, India. Study design was prospective, observational study, conducted over a period of 2 years (July 2019 to June 2021). Study approval was taken from institutional ethical committee. Pregnant women, antenatally booked at more than 20 weeks of gestation, , attending antenatal clinic and delivered at our hospital were considered for this study and were followed for maternal and foetal outcomes at the termination of pregnancy. Cases were pregnant women with bad obstetric history. Controls were low risk pregnant women with no history of any abortion. Study was explained to patients and a written informed consent was taken for participation. After inclusion in study details of subjects such as socio-demographic parameters, detailed obstetric, menstrual, medical, treatment history, clinical signs and symptoms, laboratory investigations, were recorded. General physical examination, systemic and obstetrics examination was done and findings were recorded. A fasting 5 ml venous blood sample was collected with all aseptic precautions for measurement of serum homocysteine concentration, by chemo luminescent enzyme method. Pregnant woman was considered to exposed for hyperhomocystenemia, if homocysteine value ≥15 µmol/L. Maternal and foetal monitoring was done which included NST, BPP and Doppler velocimetry. Subjects who were less than 34 weeks and required termination of pregnancy were given 4 doses of dexamethasone. Plan and mode of delivery was decided accordingly. Labour was managed partographically. Details of mode of delivery and any intrapartum or postpartum complication was recorded. All the patients were followed in postpartum period for any maternal morbidity and mortality. Maternal morbidities like hypertensive disorders of pregnancy, abruption, atonic PPH, etc. were recorded. Neonatal parameters including livebirth/stillbirth, Apgar score at 1 and 5 minutes, birth weight, sign of meconium aspiration, admission in NICU were recorded. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study 35 cases (pregnant women with bad obstetric history) and 35 controls (low risk pregnant women with no history of any abortion) were studied. Age of pregnant women was comparable in both groups; difference was not significant statistically ($p>0.05$). Other general characteristics such as gravida status, parity status were more in cases while live births were more in controls, difference was statistically significant ($p<0.001$).

Table 1: General characteristics

Characteristics	Cases (mean ± SD)	Controls (mean ± SD)	p value
Age (in years)	24.8 ± 3.4	25.3 ± 3.8	0.52
Gravida status	3.1 ± 1.3	1.2 ± 0.9	<0.0001
Parity status	2.2 ± 0.8	0.6 ± 0.4	<0.0001
Live Births	0.42 ± 0.31	1.1 ± 1.0	<0.0001

According to fasting serum homocysteine levels, among cases 67.56 % had hyperhomocystenemia (homocysteine value ≥15 µmol/L) while controls had 11.43 % subjects with hyperhomocystenemia, difference was statistically highly significant ($p< 0.001$).

Table 2: Distribution of homocysteine levels in patients studied.

Homocysteine (micromol/l)	Cases (n=35)	Controls (n=35)	p value
1-8	4 (11.43 %)	14 (40 %)	< 0.001
8.1-15	7 (20 %)	17 (40.57 %)	
15.1-20	15 (42.86 %)	3 (8.57 %)	
>20	9 (25.71 %)	1 (2.86 %)	

In present study, among cases high risk factor/ complications noted were preeclampsia (22.86 %), intrauterine growth restriction (17.14 %), abruption (8.57 %), gestational diabetes mellitus (5.71 %), HELLP syndrome (5.71 %), eclampsia (2.86 %) and acute kidney injury (2.86 %). While in cases high risk factor/ complications noted were preeclampsia (5.71 %), intrauterine growth restriction (2.86 %), abruption (2.86 %) and gestational diabetes mellitus (2.86 %). Difference for high risk factor/ complications between two groups was statistically significant. No maternal mortality noted in either group.

Table 3: High risk factor/ Complications

High risk factor/ Complications	Cases (n=35)	Control(n=35)	P- value
Preeclampsia	8 (22.86 %)	2 (5.71 %)	< 0.001
Intrauterine growth restriction	6 (17.14 %)	1 (2.86 %)	< 0.001
Abruption	3 (8.57 %)	1 (2.86 %)	< 0.001
Gestational diabetes mellitus	2 (5.71 %)	1 (2.86 %)	0.56
HELLP syndrome	2 (5.71 %)	0	-
Eclampsia	1 (2.86 %)	0	-
Acute kidney injury	1 (2.86 %)	0	-

In present study we noted a statistically significant difference in gestational age at delivery, birth weight, mean APGAR at 5 minutes, meconium passage, required resuscitation, neonate required NICU admission (%), neonates developed neonatal complications and required ventilator support between two groups. Perinatal mortality was 3 (8.57 %) (2 Stillbirth/IUD and 1 Neonatal deaths/ prematurity with low birth weight with respiratory distress).

Table 4: Perinatal outcome

Perinatal characteristics	Cases(n=35) (mean± SD)	Control(n=35) (mean± SD)	P- value
Preterm delivery	8 (22.86 %)	1 (2.86 %)	< 0.001
Gestational age at delivery (weeks)	36.1 ± 3.16	39.1 ± 2.22	<0.001
Birth weight (in Kgs)	2.21 ± 0.89	2.88 ± 0.6	<0.001
Stillbirth/IUD	2 (5.71 %)	0	--
Mean APGAR at 5 minutes	7.1 ± 2.61	8.6 ± 0.9	0.036
Meconium passage	7 (20 %)	2 (5.71 %)	<0.001
Required resuscitation	8 (22.86 %)	3 (8.57 %)	<0.001
NICU admission (%)	11 (31.46 %)	1 (2.86 %)	<0.001
Length of NICU stay (in days)	10.2 ± 9.61	5.1 ± 3.4	<0.001
Developed Neonatal complications	14 (40 %)	3 (8.57 %)	<0.001
Required Ventilator support	2 (5.71 %)	0	--
Neonatal death	3 (8.57 %)	0	--

DISCUSSION

Abnormally raised total homocysteine level during pregnancy is an established risk factor for vascular diseases resembling hypertensive disorders related of pregnancy.[3] In hyperhomocystenemia, homocysteine undergoes autooxidation generating reactive oxygen species which inactivate nitric oxide and thrombomodulin leading to endothelial damage and dysfunction.[3] The probable mechanism by which hyperhomocysteinemia affects pregnancy and placental implantation is by inhibition of trophoblast functions and cell death. Plasma homocysteine levels are determined by several factors, including blood levels of vitamin B6, vitamin B12, folate, MTHFR mutations, increased age, and hypothyroidism, which have all been suggested to be associated with RPL.[5] Choudhury SS *et al.*,[6] studied 45 pregnant women with bad obstetric history and 20 normal pregnant women. Mean serum homocysteine level in control group was 9.23 ± 3.4µmol/l and that of in bad obstetrical history (BOH) was 26.6± 5.9 µmol/l (p< 0.001). BOH group with diagnosed preeclampsia had elevated homocysteine level. There was highly significant difference in mild and severe preeclampsia, 25.6 µmol/l vs. 29.9µmol/l (p<0.001) and patients without hypertension with mild and severe disease (p<0.001). There was a relationship between level of homocysteine with adverse perinatal outcome like preterm and stillbirth (ANOVA test P<0.05). Level of homocysteine was high in BOH with FGR (p<0.05) Vaddadi Adilakshmi[7] studied 165 cases includes, 82 cases with previous history of preeclampsia ,25 cases with Placental abruption, 22 cases of Recurrent Pregnancy Loss, 21 cases with IUGR, 15 cases with Neural Tubal Defects and 50 antenatal women with previous no adverse outcome were studied in first trimester of the present pregnancy. hyperhomocysteinemi (>12 micro/L) was diagnosed in 22 out of 82 cases are with incidence rate of 26.8%, p value is 0.0001 which is extremely significant. 6 out of 25 cases with Placental abruption with incidence rate of 36.36% and p value-0. 0007. 8 out of 22 cases with Recurrent Pregnancy Loss with incidence 36.36% and p value is

0.0006. 9 out of 21 cases with IUGR with incidence rate is 42.85% and p value 0.0001. 7 out of 15 cases with Neural Tubal Defects with incidence rate 46.66% and p value 0.0001. In a comparative study by Chamotra S *et al.*,[8] mean homocysteine level of exposed group (23.26±10.77 µmol/L) was significantly higher than the unexposed group (8.99±2.47 µmol/L). Among hyperhomocysteinemic subjects, 10.5% had abruption, 15.8% had PRES and 8.7% PPH which was significantly higher than normal subjects. Similarly, patients with homocysteinemia had significantly higher proportion (21.3%) of poor Apgar score, more (41.9%) NICU admissions and higher frequency (4.7%) of meconium aspiration syndrome. Mukhopadhyay I *et al.*,[9] studied 100 pregnant women over a period of two years with history of unexplained RPL, 32% of RPL patients had hyperhomocysteinemia. Folic acid and VitB12 supplementation reduced homocysteine levels and this was found to be statistically significant. In a study conducted by Maristella *et al.*,[10] statistically significant levels of fasting total plasma homocysteine levels were found in those with RPL and unexplained sterility as compared to the control group. The median fasting total plasma homocysteine levels was 19.2 micromol/l in RPL group as compared to 7.85 micromol/l in that of study group. In a case-control study, Puri *et al.*,[11] studied 107 women with unexplained RPL and 343 fertile controls, hyperhomocysteinemia was found to be significant risk factors for RPL (OR=7.02; 95% CI 3.85-12.80). However, this study found also an association for vitamin B12 deficiency with RPL (OR 16.39; 95% CI 7.71-34.80), while folate deficiency was more common in controls (63.47%) as compared to the women with RPL (2.56%) (OR 0.015; 95% CI 0.0036-0.064) Glueck CJ *et al.*,[12] reported that 22 out of 25 women with RPL initiated a pregnancy after normalization of their homocysteine levels; 20 pregnancies resulted in a live birth, of which four were preterm and two had non-severe fetal growth retardation. No malformations, bleeding in the mother, or thromboembolic complications were reported. In patients of bad obstetric history, most of the diagnosed etiologies include endocrine abnormalities, autoimmune disorders, uterine anomalies, and genetic factors. After evaluation for these causes, approximately half of all cases will still remain unexplained. Estimation of homocysteine levels prior to pregnancy may help to predict and prevent further development of vascular disorders and adverse outcomes associated with them, if timely correction of homocysteine level is done.

CONCLUSION

In patients with bad obstetric history as well as hyperhomocystenemia, adverse obstetric outcomes such as intra uterine growth restriction, preeclampsia and abruption are more common. Also in such patients, poor perinatal outcome are expected Hyperhomocystenemia is a simple entity which can be easily diagnosed and treated.

REFERENCES

1. Eric Jauniaux,Roy G Farquharson, Ole B.Christiansen et al.Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage . Human Reproduction.2006; 21(9): 2216-22.
2. Miller AL, Kelly GS. Methionine and Homocysteine Metabolism and the Nutritional Prevention of Certain Birth Defects and Complications of Pregnancy. Alt Med Rev. 1996; 1(4): 220-235.
3. Mignini LE, Latthe PM, Villar J, Kilby MD, Carroli G, Khan KS. Mapping the theories of preeclampsia: the role of homocysteine. Obstet Gynecol. 2005;105:411-25.
4. Hague WM. Homocysteine and pregnancy. Best Pract Res Clin Obstet Gynaecol 2003;17: 459-469.
5. Bergen NE, Jaddoe VW, Timmermans S, Hofman A, Lindemans J, Russcher H, et al. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: the Generation R Study. BJOG. 2012;119(6):739-51.
6. Choudhury SS, Lokeshwari K, Das GC. Association between hyperhomocysteinemia and adverse obstetric outcome in patients with bad obstetric history. The New Indian Journal of OBGYN. 2021; 8(1): 19-22.
7. Vaddadi Adilakshmi, Incidence of Hyperhomocystenemia in antenatal women with Bad obstetric history IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), Volume 17, Issue 6 Ver. 10 (June. 2018),
8. Chamotra S, Pathania K, Verma SK, Chaudhary A. Predicting pregnancy outcomes from homocysteine level: an evidence from a North Indian study. Int J Reprod Contracept Obstet Gynecol 2020;9:1498-502.
9. Mukhopadhyay I, Pruthviraj V, Rao PS, Biswas M. Hyperhomocysteinemia in recurrent pregnancy loss and the effect of folic acid and vitamin B12 on homocysteine levels: a prospective analysis. Int J Reprod Contracept Obstet Gynecol 2017;
10. D'Uva M, Di Micco P, Strina I, Alviggi C, Iannuzzo M, Ranieri A et al. Hyperhomocysteinemia in women with unexplained sterility or recurrent early pregnancy loss from Southern Italy: a preliminary report. Thrombosis J. 2007;5(1):10.
11. Puri M, Kaur L, Walia GK, Mukhopadhhyay R, Sachdeva MP, Trivedi SS, Ghosh PK, Saraswathy KN. MTHFR C677T polymorphism, folate, vitamin B12 and homocysteine in recurrent pregnancy losses: a case control study among North Indian women. J Perinat Med 2013;41: 549-554.
12. Glueck CJ, Smith D, Gandhi N, Hemachandra K, Shah P, Wang P. Treatable high homocysteine alone or in concert with five other thrombophilias in 1014 patients with thrombotic events. Blood Coagul Fibrinolysis 2015;26: 736-742.

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