Original Research Article

Study of association between hyperhomocysteinemia and adverse obstetric outcome in patients with bad obstetric history

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Abstract

Background: Hyperhomocysteinemia is also proposed as a cause of BOH, caused by numerous factors, such as genetic defects, lack of folic acid, vitamin B6 and B12 deficiency, hypothyroidism, drugs, aging, and renal dysfunction. Present study was aimed to study the role of hyperhomocysteinemia as a cause of bad obstetric history/outcomes. **Material and Methods:** Present study was single-center, prospective, observational study, conducted in pregnant women (more than 20 weeks of gestation) attending antenatal clinic. Cases were pregnant women with bad obstetric history and controls were low risk pregnant women with no history of any abortion. A homocysteine value of ≥15 µmol/L was considered as pregnant woman exposed for hyperhomocystenemia. **Results:** In present study 40 cases and 40 controls were studied. Age was comparable in both groups and difference was not significant statistically. Gravida status and live births were significant in controls as compared to cases and difference was statistically significant. We measured fasting serum homocysteine levels and levels of ≥15 µmol/L was considered as hyperhomocystenemia. In cases 55 % had hyperhomocystenemia while controls had 20 % subjects with hyperhomocystenemia and difference was statistically highly significant (p< 0.001). In present study various high risk obstetric history was noted as H/O IUGR (20 %), H/O NTD (42.5 %), H/o Preeclampsia (57.5 %), H/O Abruption (45 %) and H/O RPL (42.5 %). Incidence of hyperhomocystenemia among them was noted as H/O IUGR (75 %), H/O NTD (70.59 %), H/o Preeclampsia (65.22 %), H/O Abruption (61.11 %) and H/O RPL (47.06 %). **Conclusion:** Hyperhomocystenemia is significantly associated with bad obstetric history as well as with high risk obstetric factors related to it such as intra uterine growth restriction, neural tube defects, Preeclampsia, Abruption and recurrent pregnancy loss.

Keywords: Hyperhomocystenemia, bad obstetric history, high risk obstetrics, Preeclampsia, recurrent pregnancy loss

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INTRODUCTION

The term bad obstetric history (BOH) is generally used for a pregnant women when her present obstetric outcome is likely to be affected adversely by the nature of previous obstetric disaster 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.[1] Homocysteine, a sulphur containing amino acid usually decreases in gestation, either due to physiological response to the pregnancy, increase in estrogen, hemodilution from increased plasma volume or increased demand for methionine by both the mother and fetus.[2] Vitamins B6 and B12 and folate acid play vital roles in influencing the functionality of homocysteine. Hyperhomocysteinemia is also proposed as a cause of BOH, caused by numerous factors, such as genetic defects, lack of folic acid, vitamin B6 and B12 deficiency, hypothyroidism, drugs, aging, and renal dysfunction.[3] In hyperhomocystenemia, homocysteine undergoes

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autooxidation generating reactive oxygen species which inactivate nitric oxide and thrombomodulin leading to endothelial damage and dysfunction. Furthermore it also interferes with fibrinolytic system adding to pathophysiology of preeclampsia and eclampsia.[4] Homocysteine causes endothelial dysfunction by various mechanisms like nitric oxide inhibition, increasing contractile prostanoids.[5] The probable mechanism by which hyperhomocysteinemia affects pregnancy and placental implantation is by inhibition of trophoblast functions and cell death. Present study was aimed to study the role of hyperhomocysteinemia as a cause of bad obstetric history/outcomes.

MATERIAL AND METHODS

Present study was single-center, prospective, observational study, conducted in Department of OBGY, Vedantaa Institute of Medical Sciences, Palghar, India. Study duration was of 1 year (January 2020 to December 2020). Study approval was taken from institutional ethical committee. Pregnant women (more than 20 weeks of gestation) attending antenatal clinic. Cases were pregnant women with bad obstetric history and controls were low risk pregnant women with no history of any abortion. A homocysteine value of ≥15 µmol/L was considered as pregnant woman exposed for hyperhomocystenemia. 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. Data were entered into Microsoft excel spreadsheet, cleaned and transferred to Epi Info version 7.2.2.6 software for analysis. Continuous variables (homocysteine levels) were presented in the form of mean ± standard deviations. 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 40 cases and 40 controls were studied. Age was comparable in both groups and difference was not significant statistically. Gravida status and live births were significant in controls as compared to cases and difference was statistically significant.

Table 1: General characteristics

Characteristics	Cases (mean ± SD)	Controls (mean ± SD)	p value
Age (in years)	26.9 ± 5.1	26.3 ± 4.8	0.65
Gravida status	3.5 ± 1.5	1.4 ± 1.1	<0.0001
Live Births	0.62 ± 0.31	1.49 ± 1.22	<0.0001

We measured fasting serum homocysteine levels and levels of ≥15 µmol/L was considered as hyperhomocystenemia. In cases 55 % had hyperhomocystenemia while controls had 20 % subjects with hyperhomocystenemia and difference was statistically highly significant (p< 0.001).

Table 2: Distribution of homocysteine levels in patients studied.

Homocysteine (micromol/l)	Cases (n=40)	Controls (n=40)	p value
1-8	6 (15 %)	9 (22.5 %)	< 0.001
8.1-15	12 (30 %)	23 (57.5 %)	
15.1-20	14 (35 %)	6 (15 %)	
>20	8 (20 %)	2 (5 %)	

In present study various high risk obstetric history was noted as H/O IUGR (20 %), H/O NTD (42.5 %), H/o Preeclampsia (57.5 %), H/O Abruption (45 %) and H/O RPL (42.5 %). Incidence of hyperhomocystenemia among them was noted as H/O IUGR (75 %), H/O NTD (70.59 %), H/o Preeclampsia (65.22 %), H/O Abruption (61.11 %) and H/O RPL (47.06 %).

Table 3: Previous obstetric history and homocysteine levels

	Number of cases (n=40)	Percentages	Number of cases with HHcy	Incidence (%)	Mean levels of Homocysteine (micromol/l)
H/O IUGR	8	20.00%	6	75.00%	15.9 ± 3.9
H/O NTD	17	42.50%	12	70.59%	16.3 ± 4.1
H/o Preeclampsia	23	57.50%	15	65.22%	17.9 ± 3.7
H/O Abruption	18	45.00%	11	61.11%	14.7 ± 4.9
H/O RPL	17	42.50%	8	47.06%	15.8 ± 4.2

DISCUSSION

Hyperhomocysteinemia has been associated with various adverse pregnancy outcomes like preeclampsia, fetal growth restriction, recurrent pregnancy loss, premature rupture of membranes and many more.[6] In a prospective case control study by Neelamma P *et al.*,[7] study group consisted of 70 pregnant women with different pregnancy complications like Pre-eclampsia, Eclampsia, unexplained Abruption, FGR with oligohydramnios and unexplained oligohydramnios and control Group was of 30 healthy pregnant women. Mean level of Homocysteine was significantly raised in all patients with pregnancy complications (study group-26.4 umol/l) compared to patients without complications (control group-8.4 µmol/L) with a p value of <0.05. Significantly a greater number of patients had Hyperhomocysteinemia in each of pregnancy complication compared to control group (p<0.05). Among them, Eclampsia group had the highest mean value of 29.40 µmol/L followed by unexplained abruption (24.60 µmol/L), Pre-Eclampsia (22.05 µmol/L), FGR with oligohydramnios (21.90 µmol/L) and unexplained oligohydramnios (20.90 µmol/L). Patients with high levels of Homocysteine also had poor pregnancy outcome. Similar findings were noted in present study. Vaddadi.A *et al.*,[8] studied 165 cases, 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. HHcy (□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. Similar findings were noted in present study. In study by Choudhury SS *et al.*, [9] out of 65 cases, 45 cases had bad obstetric history and 20 had normal pregnancy. 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 (P<0.05). Level of homocysteine was high in BOH with FGR (p<0.05). Dubey P *et al.*,[10] studied 60 patients, with 30 patients in case (history of infertility) and 30 patients in control groups. Controls included age matched parous females with at least one live birth and no history of abortions. Mean level of serum homocysteine was significantly higher in study group than normal fertile women i.e.20.5µmol/l and 10.9 µmol/l respectively. Among the patients of unexplained infertility, 22(73.3%) were found to have range above the normal healthy levels. In these patients homocysteine lowering agents were given for 6 weeks and lowering of mean homocysteine levels was observed which was 10.4 µmol/l. Six (27.3%) patients conceived spontaneously during the follow up period. Serum homocysteine levels were inversely correlated with infertility. Homocysteine lowering agents have a favourable impact on the outcome of infertility and their use is suggested in cases of unexplained infertility associated with hyperhomocysteinemia.

Study by D'Uva *et al.*,[11] revealed raised mean homocysteine levels of 21.05±8.78 micromoles /litre in 20 women with unexplained sterility,19.2±6.14µmol/l for patients with recurrent pregnancy loss versus 7.85±3.31µmol/l for controls. Their study gives an indication that infertility and recurrent pregnancy loss are a part of the continuum of the hyperhomocysteinemia induced adverse effects on female reproductive system. Mukhopadhyay I *et al.*,[12] studied 100 pregnant mothers with history of unexplained RPL. Hyperhomocysteinemia (>12 micromol/l) patients were treated with folic acid and vitamin B12 supplements and homocysteine levels were assessed again, post treatment. 32% of RPL patients had hyperhomocysteinemia. Folic acid and VitB12 supplementation reduced homocysteine levels and this was found to be statistically significant. In a case-control study by Puri M *et al.*,[13] including 107 women with unexplained RPL and 343 fertile controls, HHcy 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). Homocysteine concentrations are influenced by vitamin B status, mainly by folate and Vit B12. Therefore, vitamin B supplementation should be introduced to the pregnant women for lowering maternal homocysteine level and reducing its wide range of adverse pregnancy outcomes, including recurrent early pregnancy loss, preeclampsia, LBW, fetal loss and future risk of cardiovascular disease.[14] In the Tunisian population, 350 RPL women and 200 normal controls were tested for tHct levels, and the results of the study did not find any significant correlation

between tHct and RPL.[15] The negative association implies that RPL has a diverse etiology, which involves numerous genetic pathways. The impact of pregnancy and several lifestyle factors (vitamin intake and deficiency (vitamin B6, B12, folate), smoking, coffee and alcohol consumption, physical activity) on plasma Hcy levels further complicates research on the topic. Furthermore, we realize that there is a geographical and ethnic variation in the genetic pathways of the homocysteine metabolism.[16]

CONCLUSION

Hyperhomocystenemia is significantly associated with bad obstetric history as well as with high risk obstetric factors related to it such as intra uterine growth restriction, neural tube defects, Preeclampsia, Abruption and recurrent pregnancy loss. Hyperhomocystenemia can be easily diagnosed and treated, treatment can improve obstetric outcome.

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