THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (July-August 2012) 62(4):406–408
DOI 10.1007/s13224-012-0287-9

ORIGINAL ARTICLE

Hyperhomocysteinemia as a Risk Factor for IUGR

Pandey Kiran · Dubay Preeti · Bhagoliwal Ajay · Gupta Neena · Tyagi Geetika

Received: 23 June 2011 / Accepted: 19 June 2012 / Published online: 16 October 2012

Abstract
Objective To study the role of hyperhomocysteinemia in patients with intrauterine growth retardation.
Method 76 patients with intrauterine growth retardation were studied and compared with 50 controls which included pregnant patients without any pregnancy complications. Fasting Plasma homocysteine levels were measured and statistical analysis using tests of significance and logistic regression analysis was performed. Those in the study group were given homocysteine lowering agents for 6 wks and pregnancy outcome was studied.
Results 57.8 % women in the study group were found to have hyperhomocysteinemia. Logistic Regression analysis shows an OR of 2.45 in favor of occurrence of IUGR if homocysteine levels are raised which is statistically significant. Mean plasma homocysteine levels decreased after treatment for 6 wks but this decrease in the case of placebo group is marginal whereas the decrease in the homocysteine levels the treatment group. This implies that treatment has a definitive role in lowering of plasma homocysteine levels.
Conclusion The present study shows that hyperhomocysteinemia is associated with IUGR and should be identified as a risk factor as correction favors pregnancy outcome.

Keywords IUGR · Hyperhomocysteinemia

Pandey K. (✉), Professor and Head · Dubay P., Professor · Gupta N., Assistant Professor · Tyagi G., Resident
Department of Obstetrics & Gynaecology, G.S.V.M. Medical College, New Type IV/7, Kanpur 208002, Uttar Pradesh, India
e-mail: dr.kiranpandey@gmail.com

Bhagoliwal A., Professor
Department of SPM, G.S.V.M. Medical College, Kanpur, India

Introduction

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 the 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, and preeclampsia 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. Martinelli et al. [1] indicated an association between prothrombotic genetic factors and fetal growth retardation. Arias et al. [2] concluded that thrombophilia leading to thrombosis in maternal/fetal circulations is a significant mechanism of disease during pregnancy. Ariel et al. [3] concluded that placentas of women with severe

Table 1 Homocysteine levels in treatment group and control group

Values	Group			
	IUGR	Control	*t* value	*p* value
n	76	50	14.25	0.0001
Mean	16.4	8.14		
SD	3.37	1.90		

Odds ratio = 2.45

95 % CI of OR 1.55–3.88

Table 2 Homocysteine levels in the treatment group and the placebo group

Treatment group	Homocysteine levels	*t* value	*p* value
Before treatment	16.66 ± 1.45	8.48	0.0001
After treatment	11.76 ± 2.22		
Placebo group			
Before	17.07 ± 1.53	1.14	0.28 (N.S.)
After	16.74 ± 1.92		

Table 3 Improvement in outcome

	T/t group	Placebo group
Mean increase in AG (cm)	14.27 ± 11.57	10 ± 5.11
Mean increase in FH (cm)	6.46 ± 6.16	4.12 ± 3.16
No. of cases		
Oligohydramnios	2	8
No. of still births	0	0
No. of babies with birth weight >2.5 kg	15	8

complications and thrombophilias have an increased rate of vascular lesions, leading to impaired nutrition to the fetus.

The present study has been undertaken to study the relationship between IUGR and hyperhomocysteinemia.

Materials and methods

The present study was conducted on women attending the outpatient clinics and admitted in UISEMH, G.S.V.M. Medical College, Kanpur from January 2006 to September 2007. Taking the incidence of IUGR to be 5 %, a sample size was calculated by means of the formula ($4pq/25$) where p is the incidence and $q = 1 - p$, taking $d = 5$, i.e., a 20 % margin of allowable error. The sample size was 76. Considering the inflow of patients in our hospital, it was decided that all the patients of IUGR will form the study group. For a valid statistical comparison, a control group of 50 women was also formed which consisted of pregnant women with normal past obstetric history and no present complications. The two groups were otherwise matched and the only difference between them was the occurrence of IUGR in the study group. A detailed history was obtained, thorough examination was done, and investigations were carried out. Fasting Plasma homocysteine (Hcy) levels were measured in both the groups. Logistic regression analysis was done with probability of occurence of IUGR $P(y = 1/x)$ as the dependant variable and levels of homocysteine, Hcy (x) as the predictor variables, and Odds Ratio (OR) with 95 % CI was calculated. Those with raised plasma homocysteine levels (>15 μmol/l) were divided following a double blind random process into two groups, the treatment and placebo groups. The treatment group received homocysteine-lowering agents in the form of a combination of methylating agents and free radical scavengers for 6 weeks in addition to conventional treatment. Plasma homocysteine levels were measured again. The role of homocysteine-lowering agents on the pregnancy outcome was also studied.

Results and Discussion

The mean age in the study and in the control groups was 24.3 ± 2.85 and 22.95 ± 4.11, respectively, with a majority of women in 21–25 year age group. No significant difference was noted in the mean age of both the groups. Parity noted in the study and control groups is 2 ± 1.03 and 2 ± 1.40 and BMI is 19.63 ± 1.54 and 20.75 ± 2.18, respectively. Mean weight gain in pregnancy in the study and control groups is 4.27 ± 1.48 and 6.5 ± 1.30, respectively.

A majority of women in the study group (67.5 %) and in the control group (55 %) belonged to the middle socioeconomic status. 57.8 % of women in the study group were found to have hyperhomocysteinemia compared to none in the control group. The mean fasting plasma homocysteine level in the study group was 16.4 μmol/l ± 3.37 as compared to 8.14 μmol/l ± 1.90 in the control group.

Logistic Regression analysis shows an odds ratio = 2.45 in favor of occurrence of IUGR when homocysteine levels are raised as shown in Table 1. This value is statistically highly significant ($p = 0.0001$). The results were comparable to Regine et al. [4] who found that hyperhomocysteinemia was associated with an approximately two to threefold increased risk of IUGR. Lindbald et al. [5] studied Folate, Vitamin B12, and Homocysteine Levels in South Asian Women with Growth-retarded Fetuses and observed that the youngest women, <22 years of age, had the highest homocysteine levels and the greatest risk of IUGR (OR, 2.9; 95 % CI, 1.1–8.2) compared with the older women.

Table 2 shows that mean plasma homocysteine levels have decreased after treatment for 6 weeks, but this decrease in the case of the placebo group is marginal and statistically not significant, whereas the decrease in the homocysteine levels in the treatment group is statistically significant ($t = 8.48$; $p = 0.0001$). This implies that treatment has a definitive role in lowering of plasma homocysteine levels.

Improvement in the outcome was also studied in terms of a mean increase in AG, FH, no. of cases of Oligohydramnios, still birth, and babies with a birth weight >2.5 kg as shown in Table 3. Addition of a homocysteine-lowering agent resulted in a significant increase in the mean AG and FH at a higher rate as compared to the placebo group. This increase is satisfactory and according to the expected lines in the treatment group and not so in the placebo group. A significantly lower no. of cases of oligohydraminos and still birth were observed in the treatment group as compared to the placebo group. Similar to the results of our study, Leeda et al. [6], who studied the effects of folic acid and Vitamin B6 supplements on women with hyperhomocysteinemia and a history of IUGR, concluded that Vitamin B6 and folic acid correct the methionine loading test and improve the perinatal outcome: birth weights were 2,867 ± 648 g after treatment compared to 1,088 ± 570 g in previous pregnancies.

Conclusion

The results of our study have been successful in establishing a connection between homocysteine levels and IUGR, and therefore homocysteine levels should be identified in these women as an important risk factor. Treatment with folic acid, vitamin B6, and vitamin B12 has also been found to be helpful in therapeutic normalization and improvement in pregnancy outcome. Our study has been successful in highlighting vital research questions, and larger prospective studies are needed in this field.

References

1. Martinelli P, Grandone E, Colaizzo D, et al. Familial thrombophilia and the occurrence of fetal growth restriction. Haematologica. 2001;86:428–31.
2. Arias F, Romero R, Joist H, et al. Thrombophilia: a mechanism of disease in women with adverse pregnancy outcome and thrombotic lesions in the placenta. J Matern Fetal Med. 1998;7:277–86.
3. Many A, Screiber L, Rosner S, et al. Pathologic features of placenta in women with severe pregnancy complications and thrombophilia. Obstet Gynecol. 2001;98:1041–4.
4. Steegers-Theunissen RP, Van Iersel CA, Peer PG, et al. Hyperhomocysteinemia, pregnancy complications, and the timing of investigation. Obstet Gynecol. 2004;104:336–43.
5. Lindblad B, Zaman S, Malik A, et al. Vitamin B12, and homocysteine levels in South Asian Women with growth-retarded fetuses. Obstet Gynecol Surv. 2006;61:91–2.
6. Leeda M, Riyazi N, de vries JIP, et al. Effects of folic acid and vitamin B6 supplementation on women with hyperhomocysteinemia and a history of growth restriction or preeclampsia. Am J Obstet Gynecol. 1998;179:135–9.