IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 6 Ver. 10 (June. 2018), PP 05-09
www.iosrjournals.org

Incidence of Hyperhomocystenemia in antenatal women with Bad obstetric history

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Abstract: *The present study was conducted in King George Hospital, Andhra Medical College, Visakhapatnam from November 2014 to August 2016. Total 165 Antenatal women with bad obstetric history i.e. previous preeclampsia, placental abruption, recurrent pregnancy loss, IUGR, neural tube defects babies and 50 antenatal women with previous uneventful pregnancy outcome were included in the study. Maternal fasting serum homocysteine levels in first trimester were measured. Hyperhomocysteinemia (HHcy)is usually defined by a fasting serum value of Hcymore than 12 µmol/l.by immune assay method. Patients are thus classified as either normal or HHcy.*

Study group of 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. 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.

Combination therapy with folic acid, vit. B12, vit. B6 is effective in reducing the homocysteine levels (1). L-Methyl folate, active form of folic acid is more beneficial in cases of MTHFR mutations as it bypasses the step of methyl tetrahydrofolate reductase enzyme. In pregnancy, anticoagulation may be considered in selected cases. --

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Date of Submission: 01-06-2018 Date of Acceptance: 18-06-2018

I. Introduction

Homocysteine (Hcy) is a sulfur containing non-essential amino acid biosynthesized from the trans methylation of methionine. Normal serum levels being 5-15 micro-moles /litre.Hyperhomocysteinemia(HHcy) characterized by an abnormally high level (above 15 micro-moles /litre) of Hcy in the blood is a metabolic disorder affecting both the vascular wall structure as well as the blood coagulationsystem. It could be due to deficiency of cofactors like vitamin B6, B9, B12 or a genetic mutation resulting in enzyme deficiencies Cystathionine betasynthetase (CBS), Methylenetetrahydrofolate-reductase(MTHFR), or in enzymes involved in methyl B- synthesis. Abnormalities of methionine--homocysteine metabolismis strongly associated with intake of certain medications including anticonvulsants, cyclosporine,methotrexateand theophylline.

Its high levels are implicated in the pathogenesis of various disorders such as endothelial dysfunction, thrombosis,cardiovascular diseases, neuro psychiatric conditions, increased tendency for fracturesand even carcinogenesis. In pregnancy it is considered to be responsible for various fetal and maternalcomplications such as repeated miscarriages, pre-eclampsia, abruptio placenta, neural tubaldefects, IUGR IUD, and Venous thrombosis.

Homocysteine levels can be lowered by improving the dietary habits, supplementation with Vitamin B6, Vitamin B12, Folic acid, L-Methyl folate[2,3] Pregnant women can be offered anticoagulant therapy for a better obstetric outcome[4]. Thus, a targeted screening for HHcy mainly in antenatal women with bad obstetric history is recommended. Early and effective management of HHcy is desirable not only for obstetric purposes but also to overcome the major debilitating illnesses in the future (5).

II. Materials and Methods

This observational study conducted in Antenatal Outpatient Department ofKing George Hospital, Visakhapatnam from November 2014 to August 2016 over a period of 22 months

INCLUSION CRITERIA

Bad obstetric history implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, still birth, intrauterine fetal death, intrauterine growth retardation, congenital anomalies and early neonatal death.

- Detailed discharge summary of the events in the previous pregnancy are a pre requisite. Only documented evidence is considered.
- All antenatal women with the following history in the previous pregnancy are included in the study
- ✓ Preeclampsia
- ✓ Placental abruption
- ✓ Intra uterine growth restriction in the fetus
- ✓ Recurrent pregnancy loss
- ✓ Neural tube defects in the fetus/ child
- The antenatal women should have her pregnancy confirmed by both Urine Pregnancy test and an ultrasonography.
- Period of gestation should be < 12weeks +6 days

EXCLUSION CRITERIA

- Women with normal fetal outcome are excluded from our study.
- Women with chronic hypertension, gestational hypertension and eclampsia, gestational / type 2 diabetes mellitus, hypo/hyperthyroidism are excluded.
- History of trauma in the previous pregnancy/ smoking/ substance abuse/ fever are excluded from the study.
- Women with uterine anomalies/ cervical incompetence/ h/o cervical encirclage are excluded.
- Multifetal gestation in both present and previous pregnancies are excluded.

After obtaining informed consent from the patients, detailed history of the previous pregnancy outcome including the antenatal and postnatal period was taken, with emphasis on the nature of complication, any underlying medical conditions, fetal compromise that had occurred. Spacing between the pregnancies and the nature of inter pregnancy period were enquired. A thorough general physical examination and systemic examination done.

Pregnancy is ascertained by clinical examination, urine pregnancy test. Gestational age confirmed by ultrasound. Patients were explained regarding how the test helps in identifying the probable cause for the previous insult. If the test result is suggestive of its role in the previous bad obstetric outcome, treatment options are also made available to the patient. Patients are categorized into 5 classes

1. Preeclampsia
2. Abruption
3. IUGR
4. RPL
5. NTD

After an overnight fasting, venous blood sampling was done. Fasting first trimester blood sample is taken and plasmahomocysteine levels are noted. Sample is centrifuged immediately or kept on ice box till centrifuged. Homocysteine levels are estimated by enzyme immunoassay.

Depending on the homocysteine levels patients in the 5 classes are divided groups – those with normal levels and those with hyperhomocysteinemia, the cut off value for defining hyperhomocysteinemia being > 12 micro mole/litre.

As most of the studies focus on the comparison between cases and controls rather than incidence in a single group, incidence in our cases are mentioned, a control without any risk factors are studied for comparison, mean levels of homocysteine in both the groups are calculated and statistical test are applied whether the elevated levels in the cases are significant or not.

The statistical tests applied in our study is unpaired ‘t test, in both the cases and controls sample size and mean homocysteine is noted.

III. Results

Total 215Antenatal women, out of which 50 with previous normal pregnancy outcome and 165 women with bad obstetric history i.e. previous preeclampsia, placental abruption, recurrent pregnancy loss, IUGR and

neural tube defects babies are included in the study (exclusion criteria also to be met).

In this study the incidence of HHcy in preeclampsia was 26.8%, in placental abruption was 24%, in recurrent pregnancy loss was 36.36%in IUGR was 42.85%, and in women with previous neural tube defects babies was found to be 46.66%

Table 1: Incidence of Hyperhomocystenemia

	Total Number of cases	Number of cases with HHcy	Incidencein %
H/o Preeclampsia	82	22	26.82
H/O Abruption	25	5	24
H/O RPL	22	8	36.36
H/O IUGR	21	8	42.85
H/O NTD	15	7	46.66
Controls	50	4	8

Table 2: Comparison of mean values of Hcy in cases and control groups

	Mean Hcy levels (micromoles/L)	Range of Hcy levels (micromoles/L)
Controls	9.23	17.18 - 20.79
H/o Preeclampsia	18.7	16.2 - 88
H/O Abruption	14.15	17.15-44.15
H/O RPL	18.72	17.23-61.76
H/O IUGR	15	15.38-27.62
H/O NTD	16.8	16.8-36.8

Table 3: Statistical evaluation of Cases and Controls

	Controls	H/o Preeclampsia	H/O Abruption	H/O RPL	H/O IUGR	H/O NTD
Sample size	50	82	25	22	21	15
Incidence	8 %	26.82 %	24 %	36.36 %	42.85 %	46.66 %
Mean	9.23	18.72	14.15	18.72	15	16.8
S.D	2.54071	11.98092	2.54	18.32496	6.406810	8.15429
SEM	0.3593107	1.69436	0.35	3.90689	1.398080	2.1054286
p Value		**0.0001**	**0.0007**	**0.0006**	**0.0001**	**0.0001**

IV. Discussion

Hyperhomocysteinemia causes endothelial cell dysfunction and induces apoptotic cell death. This pathology mainly manifests as atherosclerosis, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, Alzheimer's disease, osteoporotic fractures etc. Hyperhomocysteinemia in pregnancy causes placental vasculopathy mainly leading to preeclampsia, recurrent pregnancy loss, neural tube defects, placental abruption, IUGR, IUFD[6.]

PREECLAMPSIA

There have been numerous studies that have proved a significant relation association of HHcy with preeclampsia. Pregnancy being the first step of interaction with a doctor in many women of low socio economic status and more importantly the rising rates of preeclampsia and its consequences which may range from as simple as uneventful maternal and fetal outcome to as grievous as maternal and fetal mortality and morbidity, has led to various theories for mapping the cause of preeclampsia.

Pathophysiology of preeclampsia is poorly understood but currently endothelial dysfunction is most popularly hypothesized to be a central pathophysiological feature of preeclampsia leading to altered vascular reactivity, loss of vascular integrity and activation of the coagulation cascade. Elevated homocysteine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive vascular disorders. The homocysteine-mediated vascular changes are similar to those associated with preeclampsia; therefore, it has been postulated that HHcy may be associated with this condition [7.]

Table 4: PRE ECLAMPSIA: Comparison of results with other studies

	Incidence	Mean Hcy conc.in HHcy cases (micro moles/l)	Mean Hcy conc.in controls (micro moles/l)
Present Study	26.8%,	18.7	9.23
Mariano Mascarenhas et al	16.27%	19.13	13.83
Maria G. van Pampusetal[8]	12.1%		
by G.A Dekker et.al[9]	17.7%		8.19

by Khosrowbeygi[10]et.al		14.05	6.38
by Hogue M.M et al[11]		10.57 +/- 3.39	6.86 +/- 2.47
Hasanzadeh et a1[12]		13.8+/-7	8.8+1-2.8
FatihSanlikanet. Al[13]		10.58	6.61

This difference in the incidences might be due to lesser sample size in our study when compared to other studies. In conclusion HHcy 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.

PLACENTAL ABRUPTION

Placental abruption, which manifests as either concealed or revealed antepartum hemorrhage is an important cause of feto maternal morbidity and mortality.

Table 5: PLACENTAL ABRUPTION: Comparison of results with other studies

	Incidence	Mean Hcy conc.in cases (micro moles/l)	Mean Hcy conc.in controls (micro moles/l)
Present Study	24%	14.15	9.23
Toos A.W Goddijn Wessel et.a1[14]	25%	11	9
Owen et. a1[15]	28.5%	7.9	5.1

Regine P. Steegers-Theunissen et.al[16] study had revealed a 1.3 to 4.4 times increased risk of abruption in women with HHcy compared with normal women.

RECURRENT PREGNANCY LOSS

Recurrent pregnancy loss (RPL) is defined as three or more consecutive pregnancy losses before 24 weeks of gestation. It is a major health problem and 40% of cases remain "unexplained". Pregnancy is a hypercoaguable state, but in inherited thrombophilia, the extent of this coagulability crosses the limits of the coagulation cascade, hindering the utero placental blood flow, and subsequently the fetal growth. For this reason, clotting factors are center stage for investigation into this disease.

Table 6: RECURRENT PREGNANCY LOSS: Comparison of results with other studies

	incidence	Mean Hcy conc.in cases (micro moles/l)	Mean Hcy conc.in controls (micromoles/l
Present Study	36.36%	18.72	9.23
Williane L.D.M Nelen et.a1[17]	31.5%		
A.B.C. Coumans et.a1[18]	17.1%		
MaristellaD'Uva et.a1[19]		19.2	7.85
Puri et.al[20]	65%	16.10	8.34
K.S.D Kumar et.a1[21]		10.23 pmol/l	8.95 pmo1/1
Jean Christophe gris et.a1[22]		9.4	8

INTRA UTERINE GROWTH RETARDATION

India is world's capital for low birth weight (LBW), which is ascribed to intrauterine growth restriction (IUGR) rather than prematurity. Maternal undernutrition is thought to be a major factor in the etiology of IUGR, and the undernutrition is usually thought to be a low *macronutrient intake.* Two thirds of the mothers had low vitamin B12 concentrations, folate deficiency was rare, and high circulating concentrations of homocysteine predicted IUGR.

Table 7: IUGR: Comparison of results with other studies

	incidence	Mean Hcy conc.in cases (micro moles/l)	Mean Hcy conc.in controls (micro moles/l)
Present Study	42.85%	15	**9.23**
Pandey kiran et.al [23]	**57.8%**	16.4	**8.14**
Gadhok AK et.al[24]		11.14	**7.42**
Yeter A et.a1		5.6 ± 1.9 pmol/L	4.6 ± 1.2 pmol/L
Jan Urban et al		11.50 ng/ml	9.583 ng/ml

NEURAL TUBAL DEFECTS

NTD are detected in about 300000 neonates worldwide each year, a major cause of neonatal morbidity and mortality. They are caused by abnormal closure of the embryonic neural tube between 22 and 28 days after conception. The resulting structural defects, which may occur anywhere along the neuroaxis, often leads to the postpartum exposure of neural tissue and this, in turn, may lead to severe impairment in the child's physical and mental development if child survives as many fetuses die in utero.

Table 8: NEURAL TUBAL DEFECTS: Comparison of results with other studies

	Incidence	Controls	Mean Hcy conc.in cases (micro moles/l)	Mean Hcy conc.in controls (micro moles/l)
Present Study	46.66%	8%	16.8	9.23
Quaingguet.al	40%	6.7%	15.1	8.5
Ting Zhang et.a1[25]			10.05	7.46
KoumudiGodbole et.al[46]			10.5	10.2
J.L. Mills et a1[47]			8.62 pmol	7.96

V. Conclusion

There is significant association of in antenatal women HHcy with history of preeclampsia, abruption, IUGR, RPL, neural tube defects. Targeted screening helps in identification of this biochemical abnormality which can be treated and obstetric outcome can be improved. Maternal morbidity and long term risks can also be alleviated once treatment is initiated.

References

[1]. Homocysteine and thrombosis: from basic science to clinical evidence. UndasA1, Brozek J, SzczeklikA.ThrombHaemost. 2005 Nov;94(5):907-15

[2]. Multivitamin Supplementation During Pregnancy: Emphasis on Folic Acid and L-Methyl folate. James A Greenberg, MD and Stacey J Bell, DSc, RD. Rev Obstet. Gynecol. 2011; 4(3-4): 126-127.

[3]. Aspirin and Low-Molecular Weight Heparin Combination Therapy Effectively Prevents Recurrent Miscarriage in Hyperhomocysteinemic Women PratipChakraborty, Sayani Banerjee et al. PLoS One. 2013; 8(9): e74155

[4]. Clotting disorders and placental abruption: homocysteine--a new risk factor. Eskes TK et,al. European journal of obstetrics & gynecology and reproductive biology 2001 Apr;95(2):206-12.

[5]. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. HenkJ.BlomYvoSmulder. Journal of Inherited Metabolic Disease February 2011, Volume 34, Issue 1, pp 75-81

[6]. Imbalance of folic acid and vitamin B12 is associated with birth outcome: An Indian pregnant women study. Gadjil M, Joshi k et.al European Journal of Clinical Nutrition 68, (June2014) 726-729

[7]. Clinical usefulness of plasma homocysteine in vascular disease. Graeme J Hankey, et.al Med J Aust 2004; 181 (6): 314-318

[8]. High prevalence of hemostatic abnormalities in women with a history of severe preeclampsia. Maria G. van Pampus, et.al AJOG May 1999 Volume 180, (5), Pages 1146-1150

[9]. Underlying disorders associated with severe early-onset preeclampsia - G.A. Dekkeret.al American Journal of Obstetrics and Gynecology, 1995, October Volume73(7), Pages 1042-1048

[10]. Circulating levels of homocysteine in preeclamptic women. Khosrowbeygi A, Ahmadvand H. Bangladesh Med Res Counc Bull 2011; 37: 106-109

[11]. Serum homocysteine in pre-eclampsia and eclampsia.Hoque MM. Bangladesh Med Res Counc Bull. 2008 Apr;34(1):16-20

[12]. Elevated plasma total homocysteine in preeclampsia.Hasanzadeh M, Saudi Med J. 2008 Jun;29(6):875-8.

[13]. The evaluation of homocysteine level in patientswith preeclampsia. FatihSanlikan et. al. Ginekol Pol 2015; 86. 287-291

[14]. Goddijn-Wessel et.al Eur J ObstetGynecolReprod Biol. 1996 May;66(1):23-9.

[15]. Hyperhomocysteinemia — A risk factor for abruptio placentae E. P. Owen, et.al. Journal of Inherited Metabolic Diseases 20 (1997) 359— 362

[16]. Hyperhomocysteinemia, Pregnancy Complications, and the Timing of Investigation Regine P. Steegers-Theunissen, ObstetGynecol 2004;104:336-4317. Maternal homocysteine and chorionic vascularization in recurrent early pregnancy loss WillianneL.D.M. Nelen et al., Human Reproduction2000 vol.15 no.4 pp.954-960,

[17]. Hemostatic and metabolic abnormalities in womenwith unexplained recurrent abortionA.B.C. Coumans, G.A.Dekker et .al.

[18]. Hyperhomocysteinemia in women with unexplained sterility or recurrent early pregnancy loss from Southern Italy: a preliminary report. MaristellaD'Uva, Thrombosis Journal July 20075:10.

[19]. MTHFR C677T polymorphism, folate, vitamin B12and homocysteine in recurrent pregnancy losses:a case control study among north Indian women. ManjuPuri, et.al. Journal of Perinatal Medicine 2013; 41(5): 549-554

[20]. Plasma homocysteine levels correlated to interactions between folate status and methylene tetrahydrofolate reductase gene mutation in women with unexplained recurrent pregnancy loss. K. S. D. Kumar,Journal of obstetrics and gynecology. Volume 23, 2003.,55-*58*

[21]. Antiphospholipid / antiprotein antibodies, hemostasis-related autoantibodies, and plasma homocysteine as risk factors for a first early pregnancy loss: Jean-Christophe Griset et.al.Blood Journal Republished online July 17, 2003; doi:10.1182/blood-2003-01-0320.

[22]. Hyperhomocysteinemia as a Risk Factor for IUGR. Pandey Kiran et.al. The Journal of Obstetrics and Gynecology of India (July-August 2012) 62(4):406-408

[23]. Serum homocysteine level and its association with folic acid and vitamin B12 in the third trimester of pregnancies complicated with intrauterine growth restriction..Gadhok AK, et al.; Clin Lab., 2011; 57(11-12): 933-938.

[24]. Maternal serum vitamin B12, folate and homocysteine and the risk of neural tube defects in the offspring in a high-risk area of China. Ting Zhang et al. Public Health Nutrition: 12(5), 12th June 2008 ,680-686.