WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 5, 651-660. Research Article ISSN 2277– 7105

MATERNAL SERUM HOMOCYSTEINE LEVEL IN LESS THAN 18 WEEKS PERIOD OF GESTATION AND PREGNANCY OUTCOMES

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Article Received on
26 Feb 2016,
Revised on 17 March 2016,
Accepted on 06 April 2016
DOI: 10.20959/wjpr20165-5896

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ABSTRACT

Aim: To find out correlation between increased levels of homocysteine in less than 18 weeks period of gestation and its effect on the outcome of pregnancy and to study the adverse pregnancy outcomes due to increased levels of homocysteine. **Methods:** The present study was a prospective type cohort study, comprised of 60 women at period of gestation less than 18 weeks. Serum homocysteine levels were measured and patients were followed up for the outcome of pregnancy. **Results:** A significant result was obtained in cases with spontaneous abortion, hypertension complicated pregnancy, foetal growth restriction and high homocysteine levels. Also significant result was obtained in women with history of abnormal outcome in previous pregnancy and pregnancy induced hypertension in this pregnancy and high homocysteine levels. Homocysteinemia was seen in 90% of patients with hypertension complicated pregnancy and is significant. 66.7% of patients with foetal growth restriction had homocysteinemia. 66.7% of patients with spontaneous abortion had homocysteinemia. Homocysteinemia was seen in 71.5% of patients with preterm labour but it was not found to be statistically significant. **Conclusion:** Positive correlation was obtained between elevated maternal serum homocysteine level in early pregnancy and spontaneous abortions, foetal growth restriction and hypertension complicated pregnancies.

KEYWORDS: Homocysteine; Hypertensive disorders of pregnancy; Fetal growth restriction; Spontaneous abortion.

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. Abnormalities of placental vasculature and disturbances in haemostasis can lead to inadequate foetal circulation.[1] Vascular-related pregnancy complications are a major cause of maternal and foetal morbidity and mortality.[2] The origin is thought to be related to early placentation, a process that involves trophoblast invasion and angiogenesis. One of the factors which can play an important role in the disruption of this balance is maternal hyperhomocysteinemia. Placental development in early pregnancy may be negatively influenced by increased maternal homocysteine concentrations.[2] It has also been suggested that thrombophilias like hyperhomocysteinemia augment the relative hypercoagulable state of pregnancy.[1] Normal range is considered from 5 -15µmol/L. **Adverse effects of homocysteinemia in pregnancy** are: Spontaneous Abortion, Fetal Growth Restriction, Hypertensive Disorders Of Pregnancy, Placental Abruption, Preterm Labour, Intrauterine Fetal Death, Neural Tube Defects, Other Congenital Defects.

AIM AND OBJECTIVES

To find out correlation between increased levels of homocysteine in less than 18 weeks period of gestation and its effect on the outcome of pregnancy. To study the adverse pregnancy outcomes due to increased levels of homocysteine.

MATERIALS AND METHODS

The present study was a prospective type cohort study, conducted in the Department of Obstetrics and Gynaecology, Kasturba Medical College, Mangalore, Karnataka, India. Period of the study was from February 2014 to July 2015. 60 women attending or admitted at Lady Goshen Hospital, tertiary care hospital in Dakshina Kannada, Mangaluru, at period of gestation less than 18 weeks were taken as subjects. Subjects were selected as per the inclusion criteria. All subjects were enrolled in the study after having been informed and subscribed a written consent. Detailed clinical history was taken along with other details on a detailed proforma.

Inclusion Criteria

- All the ante natal cases with period of gestation less than 18wks
- Singleton pregnancy and accurate dates

Exclusion Criteria

- Antenatal cases diagnosed with any medical condition prior to pregnancy.
- Cases taking any medication other than folic acid
- Multiple gestation

Gestational age of the patients were confirmed after taking a detailed history about the last menstrual period, date of urine pregnancy test, first clinical examination and the first ultrasound done. Only patients with accurate dating were included in the study. Patients with period of gestation less 18weeks were included in the study. Maternal serum homocysteine level was measured in the peripheral sample. These patients were then followed up till their delivery or spontaneous abortion in some cases. Detailed clinical history was taken regarding antenatal checkups, folic acid intake, ante natal complications or admissions if any, time of onset of these complications and the type of intervention done or any pre-existing morbidities. Detailed clinical examination including general physical examination, per abdomen, per speculum and per vaginal examination, where required, was done both during the time when sample was taken and at the time of outcome evaluation. Routine and specific investigations were sent that included haemoglobin, total count, platelet estimation, urine routine. Specific investigations pertaining to preterm labour like urine and high vaginal swab for culture and sensitivity, profile for hypertensive disorders of pregnancy in cases with hypertensive disorders of pregnancy. In cases with foetal growth restriction scan with doppler was done for confirmation and other causes like anaemia, hypertension and diabetes were ruled out. Patients with spontaneous abortion were grouped separately and other causes of abortion like thyroid disorders, uterine anomalies, cervical incompetence, hypertension, diabetes, urinary tract infection were ruled out. In multigravida patients, with history of abnormal outcome in previous pregnancy were categorised separately and were evaluated for any correlation between homocysteine level in this pregnancy with previous abnormal outcome and also abnormal outcome in current pregnancy, if any. 5 ml of serum was collected from the selected subjects, with all aseptic precautions after an overnight fasting. Samples were then centrifuged and serum separated and stored at -35ºC until analysis. Method used to process the sample: **CLIA method (chemo luminescence immune assay method)**. Time taken for the result: 24hours. Homocysteine level in maternal serum are obtained in terms of µmol/L from the laboratory. Homocysteine levels measured in all patients were expressed in terms of µmol/L. Normal serum levels of homocysteine were

taken as ***5 – 15µmol/L***.On the basis of the serum homocysteine levels, patients were grouped under mild, moderate and severe homocysteinemia.

- **Mild homocysteinemia – 15 – 30µmol/L**
- **Moderate homocysteinemia – 30 – 100µmol/L**
- **Severe homocysteinemia - > 100µmol/L**

Patients were then followed up till the delivery and its outcome was evaluated under following headings: **Spontaneous miscarriage / abortion**, **Foetal growth restriction**, **Hypertensive disorders of pregnancy (HDP), Placental abruption, Preterm labour, Intrauterine foetal death**, **Neural tube defects**, **Other congenital defects.**

Multigravidas with elevated level of homocysteine in this pregnancy and with abnormal outcome in this preganacy were also evaluated for previous pregnancy outcome. Homocysteine levels were then correlated with other factors like age, parity, period of gestation at delivery/abortion, outcome in this pregnancy, previous abnormal outcome.

Statistical method used for data analysis

Statistical analysis was done and Chi – square test was used to evaluate significant differences in proportion among groups. Analysis was computed using statistical package SPSS version 15. P value is expressed in correlation coefficient. $P<0.05$ – significant.

RESULTS

Total of 60 pregnant patients were taken for the study who fulfil the inclusion criteria of the study as mentioned earlier. Patients were categorised on the basis of age, parity, mode of delivery, period of gestation at delivery, pregnancy outcome. On the basis of homocysteine levels they were categorised into mild, moderate and severe. Correlation was calculated between age, parity, period of gestation at delivery, pregnancy outcome and the homocysteine levels.

3.3 % patients were less 20yrs age and maximum patients were in the age group of 26 – 30 years that is 51.6%. 58.3% patients were primigravida and 41.6% patients were multigravida. 10% patients had spontaneous abortion at less than 28 weeks period of gestation, 20% patients had preterm delivery and 70 % patients had term delivery.

Depending on the distribution of cases according to serum homocysteine levels (Table no.1) - out of 60 cases, 16 cases (26.6%) had normal homocysteine levels, 38 cases (63.4%) were found to have mild homocysteinemia, and 6 patients (10%) had moderate homocysteinemia. None of the patients were found to have severe homocysteinemia.

As per distribution according to outcome of pregnancy (Table no.2) – 18 patients (30%) had an uneventful antenatal period with normal foetal outcome. 6 patients (10%) had spontaneous abortion at less than 28weeks period of gestation. 9 patients (15%) had fetus with growth restriction. 20 patients (33.3 %) were found to have hypertensive disorders of pregnancy. 7 patients (11.6 %) reported with preterm labour. None of the patients were to have eclampsia, antepartum hemorrhage, still births and congenital anomalies in foetus.

Homocysteine levels were then correlated to various other factors which can affect the level of homocysteine during pregnancy. On comparing homocysteine levels and maternal age, period of gestation and parity – no significant correlation was obtained.

On comparing homocysteine level and normal outcome and spontaneous abortion (Table no.3), 4 patients (66.6%) spontaneous abortion were found to have elevated homocysteine level and as compared to patients with normal outcome, homocysteine level was found to be statistically significant with p value of 0.035.

Correlation between homocysteine level and normal outcome and hypertensive disorder of pregnancy (Table no.4) – 18 patients (90 %) with hypertension complicating pregnancy disorders were found to have elevated homocysteine levels and as compared to patients with normal pregnancy outcome it was found to be statistically significant with p value of 0.02942.

On comparing homocysteine level with normal outcome and fetal growth restriction (Table no.5) – 6 patients (66.6%) with fetal growth restriction homocysteine was found to be elevated and it was found to be statistically significant. None of the cases with fetal growth restriction were found to have moderate homocysteinemia. Though overall significance was not found when compared with normal outcome cases but statistical significance was seen in patients with mild homocysteinemia and fetal growth restriction with p value of 0.02.

On finding correlation between homocysteine level and normal outcome and preterm labour (Table no. 6) – 7 patients (71.5%) with preterm labour were found to have elevated homocysteine level but no positive correlation was obtained.

Previous pregnancy outcome and homocysteine level in this pregnancy

Among 60 women included in the study, 35 women are multigravida. Among these 35 women, 21 women had a normal outcome in previous pregnancy with no complications and rest 14 had history of some complication in previous pregnancy**.** Among these 14 cases (Table no.7) – 4 patients had history of spontaneous abortion, 8 cases had history of pregnancy induced hypertension, and 2 had history of preterm labour. No significant correlation was obtained between homocysteine level and patients with normal previous pregnancy outcome with P value of 0.29 (ns)

Among 14 cases with abnormal previous pregnancy outcome, 11 cases were found to have elevated homocysteine level. 6 patients with elevated homocysteine levels had HDP complication in this pregnancy whereas 4 patients had foetal growth restriction. 2 patients with normal outcome had normal homocysteine levels. P value was found to be significant only in cases with HDP in this pregnancy.

Tables and Figures

Table no. 1: Distribution according to serum homocysteine levels

Homocysteine levels	No. of pateints	Percent
Normal (5 – 15µmol/L)	16	26.6
Mild Homocysteinemia (15 – 30 µol/L)	38	63.4
Moderate Homocysteinemia (30 – 100 µmol/L)	6	10
Severe Homocysteinemia (>100 µmol/L)	0	0
Total	60	100.0

Table no. 2: Distribution according to outcome of pregnancy

Outcome	No. Of patients	Percent
Nil complications	18	30
Spontaneous abortion	6	10
Fetal growth restriction	9	15
Gestational HTN + Pre-eclampsia	11 + 9	33.3
Preterm labour	7	11.6
Eclampsia , IUD , abruption , congenital anomalies	0	0
Total	60	100.0

Table no. 3: Correlation between homocysteine level and normal outcome and spontaneous abortion

OUTCOME	Normal Hcy	Mild Hcy	Moderate Hcy
Normal N = 18	7 (39%)	11 (61%)	0
Spontaneous abortion N = 6	2 (33.3%)	2 (33.3%)	2 (33.3%)

X^2 = 6.6781 p = 0.035 significant.

Table no. 4: Correlation between homocysteine level and normal outcome and hypertensive disorders of pregnancy (HDP)

OUTCOME	Normal Hcy	Mild Hcy	Moderate Hcy
Normal N = 18	7 (39%)	11 (61%)	0
HDP N = 20	2 (10%)	14 (70%)	4 (20%)

X^2 = 7.052 p = 0.02942 significant

Table no. 5: Correlation between homocysteine level and normal outcome and fetal growth restriction (FGR)

OUTCOME	Normal Hcy	Mild Hcy	Moderate Hcy
Normal N = 18	7 (39%)	11 (61%)	0
FGR N = 9	3 (33.3%)	6 (66.6%) **X2 = 5.67 p = 0.02 sig**	0

X^2 = 0.079 p = 0.778 not significant.

Table no. 6: Correlation between homocysteine level and normal outcome and preterm labour.

OUTCOME	Normal Hcy	Mild Hcy	Moderate Hcy
Normal N = 18	7 (39%)	11 (61%)	0
Preterm Labour N = 7	2 (28.5%)	7 (71.5%) **X2 = 4.48 ,p = 0.06 ns**	0

X^2 = 0.2329 p = 0.629 not significant.

Table no. 7:

Abnormal previous pregnancy outcome – 14 cases (40%)			
Outcome in this pregnancy	**Normal Hcy (3 cases)**	**Mild Hcy (6 cases)**	**Moderate Hcy (5 cases)**
Normal	2 (66.7%)	0	0
HDP	1 (33.3%)	3 (50%)	3 (60%)
Fetal growth restriction	0	2 (33.3%)	2 (40%)
Preterm labour	0	1 (16.7%)	0

X^2 = 10.06; P = 0.12 not significant, HDP: X^2 = 3; P = 0.01 significant

DISCUSSION

Abnormalities in placental vasculature in early pregnancy and disturbance in balance between coagulation and fibrinolytic system and disturbances in foetal circulation can lead to various abnormal outcome of pregnancy[1]. One of the factors which can disrupt this balance is the elevated homocysteine levels caused to perturbations in methionine metabolism during pregnancy. In the present study 51.6% of patients were in age group of 26-30yrs. 58.4 % cases were multigravidas. 70% had term delivery and 10% had spontaneous abortion On the basis of homocysteine levels, 26.6% had normal homocysteine levels, 63.4% had mild homocysteinemia, 10% had moderate homocysteinemia. None of cases were found to have severe homocysteinemia. On the basis of outcome, 30 % cases had normal outcome, 10% had abortion, 15% had foetal growth restriction, 33.3% cases developed PIH and 11.6% had preterm labour. None of the cases were found to have abruption, eclampsia, intrauterine demise and congenital defects. In the present study no significant correlation was found between age and homocysteine level which is in agreement with another Indian study by Das et al.[3] No significant correlation was obtained between parity, period of gestation at delivery and the homocysteine level. Whereas a significant correlation was established between elevated homocysteine levels and risk of abortions (p = 0.035), risk of foetal growth restriction (p = 0.02), risk of hypertensive disorders of pregnancy (p = 0.0294). No significant correlation was obtained between elevated homocysteine levels and preterm labour. A significant correlation was obtained between elevated homocysteine levels and in cases with hypertensive disorders of pregnancy in present pregnancy with history of adverse outcome in previous pregnancies. In the study conducted by Micle O et al[4], included 18 patients with risk of abortion and 22 patients with risk of preterm birth. Higher values were obtained for

pregnancies with risk of preterm birth than those for risk of abortion. In present study significant correlation was obtained between elevated homocysteine level and spontaneous abortion.

In another study conducted by Seid Javadi et al.[5] in 2012 done to establish the relationship between maternal serum homocysteine level and the intensity of preeclampsia. Serum homocysteine level in patients with severe preeclampsia were significantly higher (P <0.001), but there was no significant difference in the mean serum homocysteine level between patients with mild preeclampsia and the control group patients (P = 0.12). The result of this study was comparable to the present study in which significant correlation was found between elevated homocysteine levels and risk of PIH (P = 0.02942).

In another study conducted by Pandey Kiran et al[1] in year 2006 about the role of homocysteinemia in patients with intrauterine growth retardation 76 patients with intrauterine growth retardation were studied and compared with 50 controls which included pregnant patients without any pregnancy complications. 57.8 % women in the study group were found to have hyperhomocysteinemia. Logistic Regression analysis shows an OR of 2.45 in favour of occurrence of IUGR if homocysteine levels are raised. Results of this study are comparable to the present study in which positive correlation was obtained between elevated homocysteine levels and foetal growth restriction, P = 0.02.

CONCLUSION

As per the results obtained in the present study it suggests that maternal homocysteinemia, in less than 18 weeks period of gestation, can be considered as one of the pathogenic factors for hypertensive disorders of pregnancy. The study also suggests that in patients with foetal growth restriction, hypertensive disorders of pregnancy and spontaneous abortion, homocysteine levels have been found to be elevated in early pregnancy.

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