

Role Of Maternal Serum Homocysteine Level on Fetal Birth Weight

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Abstract:

Objective: The present study has been conducted to investigate the role of plasma homocysteine on neonatal birth weight.

Methods: This prospective cross sectional analytical study was conducted in the inpatient department of obstetrics & gynecology, Dhaka Medical College Hospital on 120 term, singleton pregnant women. Pregnant women with plasma total homocysteine $>15 \mu\text{mol/L}$ were termed as having hyperhomocysteinemia (case, $n = 25$), while women with plasma total homocysteine $\leq 15 \mu\text{mol/L}$ were considered as normal (control, $n = 95$). Neonatal birth weight was the main outcome variable which was compared between case and control groups. **Result:** The entire women in the case group were in their 3rd decades, while 80% of the control group were in this age range and 10% was below 20 and 10% above 30 years old. The cases were older than the controls (25.6 ± 2.0 vs. 23.7 ± 4.7 years, $p = 0.051$). Over three-quarters (76%) of the cases were SSC level educated, while majority (84.2%) of the controls was primary level educated. Eighty percent of the neonates born of mothers with hyperhomocysteinemia were of low birth weight as opposed to only 9.5% in the control group. The mothers of case-group carry nearly 40(95% of CI = 11.5 – 126.4) times higher risk of having low birth weight babies than the mothers with normal homocysteine level. The mean birth weight of neonates of case group was observed to be significantly higher (2.8 ± 0.4 kg) than that of control group (2.2 ± 0.4 kg). Correlation between the two variables shows that as plasma homocysteine level of women increases the birth weight of neonates decreases bearing an inverse relationship between these two variables ($r = -0.326$, $p < 0.001$). **Conclusion:** Pregnant women with elevated plasma total homocysteine carry much higher risk of giving low birth weight babies than the women with normal or low level of total homocysteine. Thus, measuring total homocysteine during pregnancy is of much clinical importance as corrective measure could be taken to avert the adverse pregnancy outcome.

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Introduction :

The period of intrauterine growth and development is one of the most vulnerable periods in the human life cycle. The weight of the infant at birth is a powerful predictor of infant growth and survival, and is dependent on maternal health and nutrition during pregnancy. In developing countries, the majority of low birth-weight (LBW) infants because of intrauterine growth retardation (IUGR) are born small at term (> 37 weeks of gestation). Low birth weight leads to an impaired growth of the infant with its consequent risks of a higher mortality rate, increased morbidity¹, impaired mental development², and the risk of chronic adult disease. Infants who weigh 2,000-2,499 g at

birth have a four-fold higher risk of neonatal death than those who weigh 2,500-3,499 g. The more severe the growth restriction within the LBW category, the higher is the risk of death¹. Maternal nutrition is, therefore, an important factor from public health point of view because it is susceptible to public health interventions.

Realizing this concept, recently interest has turned to specific micronutrients as possible limiting factors for foetal growth. It is now known that the prevalence of vitamin B12 deficiency is high in the Indian population⁴. It may be important to look into the potential role of vitamin B12 deficiency in elevating plasma homocysteine (Hcy) levels in pregnancy, and its implications for adverse pregnancy outcomes including low birth weight⁵. Methionine synthase is an enzyme which catalyzes the methylation of homocysteine to methionine using vitamin B12 as

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B12 as a cofactor and methyltetrahydrofolate as a substrate⁶. Formation of methionine through this pathway represents an important component of the one-carbon metabolism for synthesis of phospholipids, proteins, myelin, catecholamines, DNA and RNA. A deficiency of either vitamin B12 and/or folic acid is likely to affect this pathway resulting in an elevation of plasma Hcy with a relatively low methionine level⁷. have reported that mothers in the highest tHcy (total homocysteine) tertile at 8 weeks of pregnancy had three times (OR: 3.26; 95% CI: 1.05, 10.13) and at labor had nearly four times (OR: 3.65; 95% CI: 1.15, 11.56) the odds of giving birth to a neonate in the lowest birth weight tertile. Dietary deficiencies for Vit-B6, B12, or folate are associated with elevated homocysteine concentration⁸.

Several factors increase plasma homocysteine level like genetic defects in homocysteine metabolism (CBS, MTHFR, Methionine synthase), nutritional deficiencies in vitamin cofactors (Folate, vitamin B12, vitamin B6), diseases (pernicious anemia, renal impairment, hypothyroidism, malignancy: acute lymphoblastic leukemia; carcinoma of the breast, ovary and pancreas, severe psoriasis), medications/toxins Folate antagonists- methotrexate, phenytoin, carbamazepine, vitamin B6 antagonist-theophylline, azarabine, oestrogen containing oral contraceptives, cigarette smoking, increasing age, male sex and menopause⁹. The small-for-date babies are usually ascribed to the small size and chronic undernutrition of mothers. Vitamin B12 and folate play an important role in nucleic acid metabolism cell growth and proliferation and are important determinants of fetal growth^{8,10}.

From the above background information, it is evident that circulating total homocysteine may itself increase the risk of a wide range of abnormalities. Low birth-weight is one of them. The clinical implication of the present study lies in the facts that 1) low birth weight babies are at increased risk of higher morbidity and mortality and 2) hyperhomocystenemia can usually be corrected by supplementation with B vitamins including folic acid during pregnancy. So the findings derived from the study could be extrapolated to formulate a plan for supplementation of vitamin B12 and folate to pregnant women at risk of developing hyperhomocystenemia.

Methods :

The present prospective study was carried out in the inpatient department of obstetrics & gynecology, Dhaka Medical College Hospital over a period of 2 years between January 2009 to December 2010. The study population was comprised of pregnant women at their 3rd trimesters attending Dhaka Medical College Hospital, Dhaka for antenatal check-up. Singleton pregnant women at their third trimester (between 37 – 40 weeks) with plasma total homocysteine > 15 µmol/L were considered as cases and with plasma total homocysteine ≤ 15 µmol/L were taken as controls. However, pregnant women with diabetes mellitus, chronic renal disease, chronic hypertension, preeclampsia, thyroid disease and other medical diseases or with smoking habits were excluded from the study.

A total of 120 term pregnant women admitted in the labour ward for delivery were consecutively included in the study. All the study subjects were tested for plasma homocysteine level during their stay in the hospital. Of them 25 had tHcy > 15 µmol/L (designated as Case) and the rest 95 had tHcy ≤ 15 µmol/L (Control). Neonates weighing < 2500 g at birth were termed as low birth-weight (LBW). Quantitative measurement of serum total homocysteine was estimated by fluorescence polarization immunoassay (FPIA) method by Abbott AxSYM system analyzer¹¹.

Collected data were processed using software SPSS (Statistical package for social sciences) version 11.5. The test statistics used to analyse the data were descriptive statistics, Chi-square (χ^2), Student t-Test and Odds Ratio with 95% confidence interval. Spearman correlation was done to see the relationship between maternal plasma homocysteine and neonatal birth weight. Level of significance was set at 0.05 and p-value < 0.05 was considered significant.

Result :

Age distributions of the study subjects demonstrate that all the women in the case group were in the range of 20 – 30 years, while 80% of the control groups were in this age range and 10% was below 20 and 10% above 30 years of

age. The cases were a bit older than the controls (25.6 ± 2.0 vs. 23.7 ± 4.7 years, $p = 0.051$). More than three-quarter (76%) of the cases were SSC level educated while majority (84.2%) of the controls was primary level educated. Cases were mainly rural residents (64%) and the rest 36% were urban residents. Forty percent of the controls were from semi-urban area, 34.7% from rural and 25.3% from urban area (Table I).

Eighty percent of the cases gave birth to low birth weight neonates as opposed to only 9.5% of the controls. The risk having low birth weight babies in case group is more than 38(95% of CI = 11.5 – 126.4) times higher than that in the control group. The mean birth weight of neonates of mothers with hyperhomocysteinemia (serum homocysteine > 15 nmol/L) was observed to be significantly higher (2.8 ± 0.4 kg) than that of mothers having normal homocysteine level (2.2 ± 0.4 kg) (Table II). Correlation between the two variables shows that as plasma homocysteine level of women increases the birth weight of neonates decreases giving an inverse relation between the variables of interest ($r = -0.326$, $p < 0.001$) (fig. 1–2).

Table-I

Comparison of demographic features between case and control groups

Demographic Features	Group		p-value
	Case (n %)	Control (n %)	
Age* (yrs.)			
< 20	0(0.0)	9(9.5)	
20 – 30	25(100.0)	76(80.0)	
>30	0(0.0)	10(10.5)	

Table II

Association between plasma homocysteine and birth weight of baby

Birth weight (kg)	Group		Odds Ratio (95% CI of OR)	p-value
	Case (n = 25)	Control (n = 95)		
< 2.5	20(80.0)	9(9.5)	38.2 (11.5-126.4)	< 0.001
≥ 2.5	5(20.0)	86(9.5)		

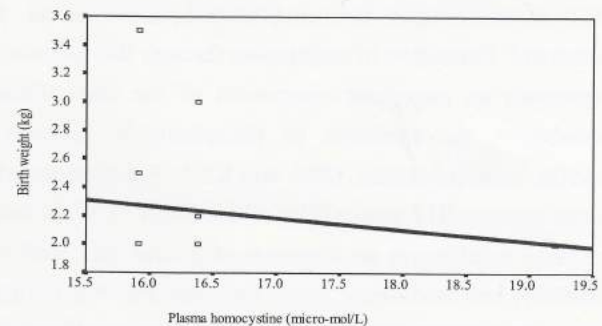


Fig. 1: Correlation between plasma homocysteine and birth weight of neonates (case group)

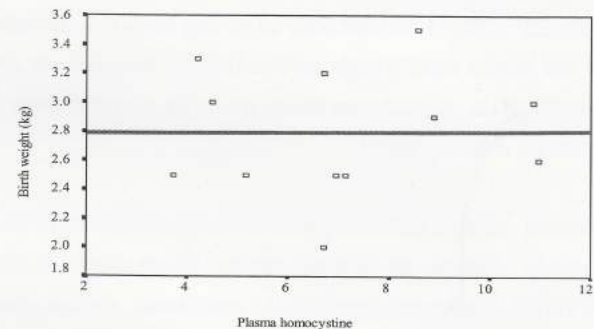


Fig. 2: Correlation between plasma homocysteine and birth weight of neonates (control group)

Discussion :

The present study aimed at finding the association between the level of maternal homocysteine at term and neonatal birth weight included a total of 100 samples with single tone uncomplicated pregnancy. The study showed that pregnant women with hyperhomocysteinemia (< 15 $\mu\text{mol/L}$) had neonates with mean birth weight 2.8 kg, while mothers with normal homocysteine level (> 15 $\mu\text{mol/L}$) had babies with average birth weight 2.2 kg. Eighty percent of the babies born to hyperhomocysteinemic mothers were of low birth weight as opposed 10% of the babies born to mothers with normal homocysteine level. The risk of delivering a low birth weight baby by pregnant women with hyperhomocysteinemia was nearly 40(95% of CI = 11.5 – 126.4) times higher than that by the mothers with normal homocysteine. This is in line with the studies done by Lindblad et al¹² and Vollset et al⁵. Another study done by Yajnik et al¹³ in India reported the higher plasma tHcy concentrations were associated with lower birth weight. Murphy and associates⁷ in their study demonstrated that neonates of mothers in the highest tHcy tertile at 8 weeks of pregnancy had 3-fold (OR: 3.26; 95%

CI: 1.05, 10.13) and at labor had nearly four times (OR: 3.65; 95% CI: 1.15, 11.56) higher risk of giving birth to a neonate in the lowest birth weight tertile. Neonates of mothers in the highest tHcy tertile at labor weighed on an average 228 g less than those of mothers in the low and medium tertiles. They also showed that supplemented (with folate and vitamin B12) mothers had lower tHcy at labor than unsupplemented mothers, as did their neonates. Maternal and fetal tHcy was significantly correlated throughout the study. Neonates of mothers in the highest tertile of homocysteine weighed less. Supplemented mothers had lower tHcy at labor than unsupplemented mothers, as did their neonates. These findings are also consistent with findings of the present study where plasma homocysteine level of pregnant women and birth weight of neonates exhibited an inverse relationship indicating that higher the level of homocysteine the lower is the birth weight ($r = -0.326$, $p < 0.001$).

Shirin and associates¹⁴ in an attempt to find the association between plasma Hcy in pregnant women and IUGR enrolled 80 pregnant women with 30 having fetus with IUGR (case) and 50 without IUGR (control). Maternal Hcy of all the subjects were measured at 3rd trimester and its effects on neonatal size were analyzed. The maternal Hcy of the IUGR cases was significantly higher than the controls. The IUGR babies born to cases had a significantly lower birth weight compared to the babies born to control mothers. The study concluded that raised homocysteine might be one of the risk factors for IUGR. In a prospective population-based study conducted near Pune (PMNS) between 1993-96, serum homocysteine level was measured in mothers of full-term small for gestational age (SGA) babies (< 10th centile) and in mothers of appropriate for gestational age (AGA) babies (> 10th centile). Mothers of SGA babies were lighter and shorter than those of AGA babies ($p < 0.05$, both) and had higher plasma tHcy concentration ($p < 0.01$). Total homocysteine concentrations were inversely related to plasma vitamin B12 and red cell folate concentrations ($r = -0.5$, $p < 0.01$, both). Higher maternal plasma tHcy concentration was significantly associated with lower offspring birth weight ($r = -0.28$, $p < 0.05$ adjusting for maternal height, weight, gestation at delivery and the baby's gender). This effect was reduced by adjustment for red cell folate concentration. Other investigators also showed that mothers of SGA

babies had higher plasma homocysteine concentration^{15,16}. It may, therefore, be important to look into the potential role of vitamin B12 deficiency in elevating plasma homocysteine (Hcy) levels in pregnancy, and its implications for adverse pregnancy outcomes including low birth weight. Methionine synthase is an enzyme which catalyzes the methylation of homocysteine to methionine using vitamin B12 as a cofactor and methyltetrahydrofolate as a substrate⁶. Formation of methionine through this pathway represents an important component of the one-carbon metabolism for synthesis of phospholipids, proteins, myelin, catecholamines, DNA and RNA. A deficiency of either vitamin B12 and/or folic acid is likely to affect this pathway resulting in an elevation of plasma Hcy with a relatively low methionine level.

One of our weaknesses in this study is the failure of maternal B12 and folic acid status assessment because of financial constraint. If we could do the cord blood assessment of B12, folic acid and Hcy, probably it would make out much better pathophysiological picture over this issue. We are optimistic that, in spite of these shortcomings the conclusions derived from this study on our population at least has given a tangible pulse of this big health problem and has created the window to visualize and conceptualize the magnitude of the problem.

The study concludes that pregnant women with elevated plasma total homocysteine carry much higher risk of giving low birth weight babies than the women with normal or low level of total homocysteine. Thus, measuring total homocysteine during pregnancy is of much clinical importance as corrective measure could be taken to avert the adverse pregnancy outcome.

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