Original Article:

Folic acid deficiency related to hyperhomocystinemia has less correlation with Gestational Diabetes Mellitus (GDM)

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Abstract

Gestational diabetes mellitus (GDM) is a different degree of the glucose intolerance that begins during pregnancy. GDM affects maternal and child health and is associated with a potential for preeclampsia, caesarean delivery due to macrosomic baby and type 2 diabetes in the mother, and with higher rates of perinatal mortally and many abnormalities in the infant. Homocysteine is a naturally occurring amino acid. Hyperhomocysteinemia(Hcy) is increased homocysteine levels which are associated folic acid deficiency. Hcy is regulated by several factors including genetically determined metabolic enzyme alteration, nutritional status, underlying disease, certain medication, age and pregnancy. A total of (40 case+40control) 80 patients are included in this study, it was observed that majority 21(52.5%) patients were age belonged to 31-35 years in case group and 17(42.5%) patients were age belonged to 31-35 years in control group. The mean age was found 30.5±4.2 years in case group and 29.05±4.2 years in control group. Majority 19(47.5%) patients had 3rd gravida in case group and 20(50.0%) patients had 3rd gravida in control group. Majority patients BMI belonged to 25-29.9 kg/m^2 (over weight) in both groups which was 21(52.5%) in case and 32(80.0%) in control group. The mean BMI was found 28.9±3.4 kg/m^2 in case and 28.53±2.9 kg/m^2 in control group. The difference was not statistically significant (p>0.05) between two groups. Studies have shown that folate deficiency is associated with increased homocysteine levels in blood.

Keywords: Gestational diabetes mellitus (GDM), Hyperhomocysteinemia(Hcy)

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Introduction:

Gestational diabetes mellitus (GDM) is a common condition which is defined as a different degree of the glucose intolerance that begins or first detected during pregnancy. Maternal diabetes in pregnancy, ie gestational diabetes mellitus, type 2 (Type2DM and type 1 diabetes, is the most common medical complication of pregnancy

and can lead to serious consequences for both the mother and the child. Diabetes in pregnancy increased by 4.3-13.3% in Bangladesh (Al Mamun et al. 2012)[2].

Homocysteine is a naturally occurring amino acid. In normal functioning metabolic state, methionine produces homocysteine as an intermediate step before either trans-sulfuration via cystathionine into cysteine or remehyhlation to methionine.

Hyperhomocysteinemia is elevated level of homocysteine has been detected in patients with type 1 and type 2 diabetes and is associated with premature atherosclerosis, which is associated with a number of pregnancy complication, such as neural tube defect, repeated miscarriages, abruption placentae, fetal death, preeclampsia and IUGR (Lopez-Quesada, 2003)[10].

Folate deficiency is also a common cause of hyperhomocysteinemia. Supplementation with folic acid and Vit B_6 has been applied with some beneficial effect in pregnancy with a history of intrauterine growth retardation and preeclampsia (RCOG 2003)[14]. Our Studies at BSMMU shown that levels of Hcy generally lower during pregnancy, either due to physiological response to the pregnancy as increase in estrogen, hemodilution from an increase plasma volume, or increased demand for methionine by both mother and the felus. Previously folic acid administration has been shown to reduce Hcy levels in healthy subject and patients with renal and vascular disease.

Folic acid, Vit B_{12} and Vit B_6 are all cofactors in Hcy metabolism. Hence during gestational diabetes, Hcy levels might increase. Serum Vit B_{12} and folic acid levels are known to decrease during GDM. (Vambergue et al. 2002)[16].

Hyperhomocysteinemia, as a major independent risk factor for vascular disease, has been found in some studies to be associated with clinical condition of insulin resistance (Meigs et al. 2001)[11]. In different studies it is shown that hyperhomocysteinemia was associated with Hyperinsulinemia. According to Bangladesh Health and disease research center for rural peoples shown GDM complications is increased by 4.3-13.3% (Al Mamun et al. 2012)[2].

Some studies showed that elevation of homocysteine present in women with GDM that is more prominent in women with impaired GTT and shows significant correlation with history of GDM.

Aim of the present study is to see the association between high levels of homocysteine with GDM. From the knowledge of the study preventive measures can be taken by reducing its level with simple measure by taking folic acid and vitamin supplement in antenatal as well as in preconceptual period.

OBSERVATION AND RESULTS:

Table I: Demographic variable of the study population (n=80)

Demographic variable	Case (n=40)		Control (n=40)		*P* value
	n	%	n	%	
Age (in years)					
≤20	2	5.0	3	7.5	
21-25	5	12.5	8	20	
26-30	10	25.0	12	30	
31-35	21	52.5	17	42.5	
>35	2	5.0	0	7.5	
Mean± SD	30.5±4.2		29.05±4.2		[a]0.126[ns]
Range (min-max)	(20-36.0)		(20-35.0)		
Gravida					
Primi	10	25.0	7	17.5	
2nd	11	27.5	13	32.5	[b]0.697[ns]
3rd	19	47.5	20	50.0	
BMI (kg/m^2)					
Normal (18.5-24.9)	6	15.0	3	7.5	
Over weight (25-29.9)	21	52.5	32	80.0	
High risk (≥30)	13	32.5	5	12.5	
Mean± SD	28.9±3.4		28.53±2.9		[a]0.602[ns]
Range (min-max)	23-39.0		24-39.0		

ns= not significant
[a]P value reached from unpaired t-test
[b]P value reached from chi square test

A total of 80 patients were included in this study, it was observed that majority 21(52.5%) patients were age belonged to 31-35 years in case group and 17(42.5%) patients were age belonged to 31-35 years in control group. The mean age was found 30.5±4.2 years in case group and 29.05±4.2 years in control group. Majority 19(47.5%) patients had 3rd gravida in case group and 20(50.0%) patients had 3rd gravida in control group. Majority patients BMI belonged to 25-29.9 kg/m^2 (over weight) in both groups which was 21(52.5%) in case and 32(80.0%) in control group. The mean BMI was found 28.9±3.4 kg/m^2 in case and 28.53±2.9 kg/m^2 in control group. The difference was not statistically significant (p>0.05) between two groups.

Table II: Distribution of risk factor for gestational diabetes mellitus (n=80)

Family history of DM	Case (n=40)		Control (n=40)		OR	Adjusted OR
	n	%	n	%		
Present	27	67.5	4	10.0	18.69	16.77
Absent	13	32.5	36	90.0		
Homocystein Mean±SD	6.51±0.25		7.9±0.29		37.0%	33.0

Result is significant at 5.0% level of CI

Family history of diabetes mellitus was found 27(67.5%) in case and 4(10.0%) in control group with Mantle-Haenszel Common Odds Ratio Estimate 18.69 and adjusted OR 16.77. Mean Homocystein level was found 6.51±0.25 μmol/L in cases and 7.9±0.29 μmol/L in control group. The difference was statistically significant ($p<0.05$) between two groups. Since serum Homocystein level is a quantitative variable, a decrease in one unit of serum Homocystein level has 33.0% increase in odds of having gestational diabetes mellitus.

Table III: Distribution of the study patients according to risk factors (n=80)

Risk factors	Case (n=40)		Control (n=40)		*P* value
History of preterm delivery					
Present	15	37.5	0	0.0	0.001[s]
Absent	25	62.5	40	100.0	
History of congenital anomaly in previous pregnancy					
Present	5	12.5	0	0.0	0.027[s]
Absent	35	87.5	40	100.0	

Regarding the risk factors of the study patients, it was observed that 15(37.5%) patients had history of preterm delivery in case but not found in control group. History of congenital anomaly in previous pregnancy was found 5(12.5%) in case but not found in control group. The difference was statistically significant ($p<0.05$) between two groups.

DISCUSSION:

This prospective observational study was carried out with an aim to evaluate the association of serum homocysteine level with gestational diabetes mellitus and to determine the blood glucose level in

pregnant women of 24 weeks upto 40 weeks and also find out the serum homocysteine level in glucose tolarent pregnant women and glucose intolarent pregnant women in 24 weeks upto 40 weeks.

Several studies reveal that elevated level of homocysteine was found in women of gestational diabetes mellitus. As maximum of the study population were of middle class family and taking vegetables in diet, rich in folate supplement. High folic acid level helps in decreasing the level of homocysteine. Some of the studies were found where lower levels of homocysteine were found associated with GDM.

In this present study it was observed that multigravida was predominant in both groups, where 47.5% were in 3rd gravida in case group and 50.0% in control group were in 3rd gravida. The difference was not statistically significant ($p>0.05$) between two groups. Similar findings were also found by Ananth et al. (2007)[3] and Koebnick et al (2002)[9].

In this study it was observed that most of the patient's BMI belonged to 25-29.9 kg/m^2 (over weight) in both groups, which was 52.5% in case and 80.0% in control group. The mean(SD) BMI was found 28.9(3.4) kg/m^2 varied from 23.0 to 39.0 kg/m^2 in case and 28.53(2.9) kg/m^2 varied from 24.0 to 39.0 kg/m^2 in control group. The mean BMI difference was not significant ($p>0.05$) between two groups. In another study, E. Lopez-Quesada et al. (2003)[10] found the mean(±SD) BMI was 26.3 kg/m^2 varied from 19.3 to 37.2 kg/m^2 in case and 25.6 kg/m^2 varied from 18.4 to 38.5 kg/m^2 in control group. On the other hand, though some authors have found normal BMI (Ananth et al. 2007[3]; Koebnick et al 2002[9]; Murphy et al 2002[13]; Vermeulen et al. 2000[17]; and Agardh et al. 1994[1]) which may due to that they enrolled early gestational age in their study patients.

In this series it was observed that family history of diabetes mellitus was found 67.5% in case and 10.0% in control group. 37.5% patients had history of preterm delivery in case but not found in control group. History of congenital anomaly in previous pregnancy was found 12.5% in case but not found in control group. Family history of diabetes mellitus, preterm delivery history and history of congenital anomaly in previous pregnancy were significantly ($p<0.05$) higher in cases group. Hernandez-Diaz et al. (2002)[7] showed 11.4% patients had family history of DM. In another study Vermeulen et al. (2000)[17] obtained 5.3% and 3.8% patients had previous family history of DM.

Homocysteine is a naturally occurring amino-acid that has become the subject of much research interest. In this current study it was observed that the mean(SD) serum homocysteine level was 6.51(0.25) µmol/L in case and 7.9(0.29) µmol/L in control group, which were significantly ($p<0.05$) lower in case group. On the other hand Hassan et al. (2008)[6] observed that the mean serum homocysteine concentration in women with GDM was significantly higher than that in normal pregnant controls between 24-28 weeks gestation (6.11±0.54 µmol/L and 4.29±0.27 µmol/L respectively; $p<0.001$). Guiseppe et al. (2003)[4]; Tarim et al. (2006)[15]; Mohamadi et al. (2009)[12]; have also made almost identical observations. Also, Guven et al. (2006)[5]found higher homocysteine levels GDM patients

compared to normal pregnant women, which were 9.0±3.1 μmol/L and 7.4±1.6 μmol/L respectively. The plasma homocysteine concentration is regulated by several factors, including genetically determined metabolic enzyme alterations, nutritional status, underlying diseases, certain medications, age and pregnancy (Walker et al. 1999)[18]. However, in this current study GDM cases had significantly lower homocysteine level with compared to normal pregnancy.

Conclusion:

This study was undertaken to evaluate the association of serum homocysteine level with gestational diabetes mellitus. Majority of the patient's age belonged to 31-35 years in both groups. Multigravida was predominant in both groups. Height, weight and BMI were similar between two groups. Family history of diabetes mellitus, preterm delivery history and history of congenital anomaly in previous pregnancy were significantly ($p<0.05$) higher in case group. From this study it was found that a decreased level of homocysteine and positive family history of diabetes are risk factors for gestational diabetes mellitus. Dietary habit in study groupcould be a cause of lower level of homocystine.

Limitation:

The study was done in a single center and within a limited period of time.

Recommendation:

Further outcome from the study on hypohomocysteinemia is associated with gestational diabetes mellitus, is recommended on a large study population, provided with the study population from rural areas.

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