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Association of Vitamin B12 with Gestational Diabetes Mellitus

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ABSTRACT

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Background: Gestational diabetes mellitus is one of the most common metabolic disorders during pregnancy and associated with increased maternal and neonatal morbidities. Low serum vitamin B 12 level have been associated with the risk of developing gestational diabetes mellitus (GDM). **Objectives:** The aim of this study was to find out any association of serum vitamin B12 with GDM. **Methods:** This cross-sectional comparative study was conducted in the department of Obstetrics and Gynaecology, BSMMU during October, 2017 to February, 2020. A total of 86 pregnant women between 18 to 40 years of age attended antenatal clinic and admitted in hospital in their 29 to 40 weeks of pregnancy were included in this study from 211 pregnant women. Among them 43 diagnosed cases of GDM were considered as group A and rest 43 without GDM were considered as group B. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24). **Results:** Serum vitamin B12 concentration was measured. The mean serum vitamin B12 level was 148.88±13.91 in group A and 182.70±27.16 in group B. The mean vitamin B12 level was statistically significantly low in GDM group than non GDM group (p=0.001). There was a significant negative correlation of serum vitamin B12 level with fasting plasma glucose (r=-0.561, p<0.001) and plasma glucose 2 hours after 75g glucose in GDM patient (r=-0.258, p=0.017). Therefore, low

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serum vitamin B12 can be regarded as a significant risk factor for the development of GDM. **Conclusion:** The association of Vitamin B12 with gestational diabetes mellitus (GDM) generally highlights that low Vitamin B12 levels may be associated with an increased risk of developing GDM. Vitamin B12 levels during pregnancy may play a role in reducing the risk of GDM. Regular monitoring and possible supplementation in deficient women could be beneficial as part of prenatal care.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a common medical disorder of pregnancy. The prevalence of GDM is increasing day by day in the world. The prevalence is 1 to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed. [1] In Bangladesh, the prevalence of GDM is 9.7%. It is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. [2] Hyperglycemia first detected at any time during pregnancy is classified as either: Diabetes mellitus in pregnancy or gestational diabetes mellitus (GDM). GDM is diagnosed when fasting plasma glucose is 5.1-6.9mmol/L, or 1hour plasma glucose is 10.0mmol/L and 2 hours plasma glucose is 8.5-11.0mmol/L following a 75g oral glucose load. [3]

Different risk factors are responsible for developing of GDM like Obesity, increasing maternal age, history of GDM and macrosomic baby in previous pregnancy, history of still birth or abortion, history of diabetes in 1st degree relatives, and certain Asian and African ethnic women at a higher risk of developing GDM. [3]

The main cause of developing GDM is not clearly understood. Pancreatic β-cell dysfunction and insulin resistance is considered as underlying pathology of developing GDM. The physiologic result of insulin resistance is increased insulin secretion by the pancreatic β-cells. In case of normal pregnancy, the progressive insulin resistance causes increase insulin secretion by the pancreatic β-cells to maintain glucose homeostasis. In case of GDM, the pregnant women fail to secret excessive insulin to compensate for the increased insulin resistance, resulting in β-cells deterioration and hyperglycemia. [1] The pregnancy is a state of insulin resistance and the mechanism of this is not clearly understood. The major focus was on feto-placental unit and the hormones secreted during pregnancy like estrogen, progesterone, cortisol, and placental lactogen. These hormones are increased in pregnancy and increase as pregnancy advances and are thought to mediate insulin resistance. [4]

Vitamin B12 is an essential water-soluble vitamin. It plays an important role in different physiological procedure in the body like production of erythrocytes and optimal nervous system function. Vitamin B12 deficiency occurs due to lack of dietary source and increased cell turn over. The deficiency of vitamin B12 can produce different symptoms If not diagnosed and treated early, different symptoms manifest within a short period of time and its deficiency can be treated by cobalamin therapy. [5] Pregnant women are at an increased risk of vitamin B12 deficiency if dietary requirements are not met. Because they are in a state of high cellular turnover and requirement of vitamin B12 is also increased because growing fetus consumes vitamin B12 from the mother's body. Low level of maternal vitamin B12 is associated with increased risk of neural tube defect and excess adiposity, increased insulin resistance and impaired

neurodevelopment. These offspring are also in increased risk of development of cancer in the future. [6]

In pregnancy prevalence of vitamin B12 deficiency in Bangladesh is 46%. [7] Various international studies have recently hinted towards an association of vitamin B12 deficiency with GDM. In vitamin B12 deficiency cellular folate is trapped as inactive 5-methyltetrahydrofolate. [8] This results in impaired methionine and protein synthesis, which may prevent lean tissue deposition. Decreased conversion of methymalonic acid to succinyl co A, for which vitamin B12 acts as a rate limiting coenzyme, results in the accumulation of methylmalonic acid and may increase lipogenesis and insulin resistance. And insulin resistance cause GDM.

Early detection and treatment of GDM prevent maternal and fetal complications. So, it is necessary to develop biochemical markers to fulfill this need. [9] Vitamin B12 level act as such a marker. Furthermore, sufficient data are not available on the relationship between serum vitamin B12 level concentrations during pregnancy and insulin resistance, and also the risk of subsequent development of GDM. So, the primary aim of this study is to determine serum vitamin B12 in GDM and normal pregnant women and find out any association between two groups.

METHODOLOGY

This cross-sectional study was carried out in the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU) during October, 2017 to February, 2020. A total of 86 pregnant women were participated in the study and they attended the antenatal clinic and admitted in the Department of Obstetrics and Gynaecology. Among them 43 diagnosed cases of GDM were considered as group A and rest 43 without GDM were considered as group B. Selections of the patients were done according to the inclusion and exclusion criteria by history taking, thorough physical examinations and proper investigations. Maintaining selection criteria and after taking informed written consent data were collected through a semi structured questionnaire. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

RESULTS

Table 1: Age distribution of the study population (N=86).

Age (years) (18-40) years	Group-A n=43	Group-B n=43
Mean ±SD	**27.00±3.80**	**24.91±4.77**

Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

The mean age of study population of group A was 27.00±3.80 years and in group B were 24.91±4.77 years.

Table 2: Difference in the parity of the study subjects (N=86)

Gravida	Group A (n=43) No. (%)	Group B (n=43) No. (%)
Primigravida	10(23.26)	19(44.19)
Multigravida	33(76.74)	24(55.81)

Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

Both in group A and in group B maximum of the study subjects were multigravida. In group A 10(23.26%) pregnant women were primigravida and 33(76.74%) cases were multigravida. In group B, 19(44.19%) pregnant women were primigravida and 24(55.81%) pregnant women were multigravida.

Table 3: Difference of the BMI in study subjects (N=86)

BMI	Group A (n=43) n (%)	Group B (n=43) n(%)
<18.5	0(0.00)	03(7.00)
18.5-24.9	16(37.20)	29(67.40)
25-29.9	23(53.50)	09(20.90)
>30	04(9.30)	02(4.70)

Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

In group A maximum 23(53.50%) of the study subjects were in 25-29.9kg/m^2BMI group. And in group B maximum 29(67.40%) of the study subjects were in 18.5-24.9kg/m^2 BMI group. In group A no pregnant woman had BMI <18.5kg/m^2. In group A, 16 (37.20%) pregnant women were in 18.5-24.9kg/m^2 BMI group and 04(9.30%) were in >30 kg/m^2BMI groups. In group B 03(7%) pregnant women were in <18.5kg/m^2 BMI group, 09(20.90%) pregnant women were in 25-29.9kg/m^2 BMI group and 02(4.70%) were in >30kg/m^2 BMI group.

Table 4: Difference in the mean gestational age of the study subjects (N=86)

Mean gestational age	Group A (n=43)	Group B (n=43)
Mean (Weeks)	36.16±1.49	35.47±2.23

Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

In group A mean gestational age was 36.16±1.49 weeks and in group B mean gestational age was 35.47±2.23 weeks.

Table 5: Difference of the plasma glucose level in study subjects (N=86)

Plasma glucose level	Group A (n=43)	Group B (n=43)	p-value
Fasting plasma glucose (mmol/l)	6.06±0.38	4.60±0.27	<0.001
2 hours after 75 gm glucose (mmol/l)	8.89±1.42	7.31±1.29	<0.001

Student t test was performed to compare the mean plasma glucose level of both groups
Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

Both (fasting and 2 hours after 75 gm glucose) mean plasma glucose level was statistically significantly more in group A than group B(p<0.001). In group A mean fasting plasma glucose level was 6.06±0.38mmol/l and in group B mean fasting plasma glucose level was 4.60±0.27 mmol/l. In group A, mean plasma glucose level 2 hours after 75mg glucose were 8.89±1.42 mmol/l and in group B the mean was 7.31±1.29 mmol/l.

Table 6: Difference of the Vitamin B-12 status in study subjects (N=86)

Vitamin B-12	Group A (n=43) No. (%)	Group B (n=43) No. (%)	p-value	Vitamin B-12
≤ 150 p gm/ml	13(30.23)	05(11.63)	0.031	≤ 150 p gm/ml
>150 p gm/ml	30(69.77)	38(88.37)		>150 p gm/ml

Chi-squared Test (c^2) was performed to compare between two groups
Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

In group A 13(30.23%) study subjects had vitamin B12 level ≤ 150 p gm/ml and in group B only 05(11.63%) study subjects had vitamin B12 level ≤ 150 p gm/ml. The percentage of study subjects having vitamin B12 level ≤ 150 p gm/ml was statistically significantly more in group A than group B (p=0.031).

Table 7: Difference of the mean vitamin B12 level in study subjects (N=86)

Vitamin B-12	Group A (n=43)	Group B (n=43)	p-value
Mean (p gm/ml)	148.88±13.91	182.70±27.16	0.001

Student t test was performed to compare the mean vitamin B12 level of both groups
Group A: Pregnant women with GDM
Group B: Pregnant women without GDM

The mean vitamin B12 level in group A was 148.88±13.91 p gm/ml and in group B the mean was 182.70±27.16 p gm/ml. The mean vitamin B12 level was statistically significantly low in group A than group B (p=0.001).

Table 8: Multivariate analysis of risk factors for GDM (N=86)

Variables	Odds ratio	95% CI	p-value
Vitamin B12	4.47	0.513 – 0.952	0.023
Age	0.98	0.852 – 1.12	0.720
BMI	0.70	0.968 – 1.36	0.114
Parity	0.65	0.19 –2.20	0.488
Gestational age	1.15	1.11 – 18.00	0.0350

Multivariate regression analysis of different risk factors for developing of GDM was done. Vitamin B12 and gestational age was found to be independently associated with vitamin B-12 deficiency (p<0.05). Vitamin B12 OR of 4.47 (95% CI 0.513 – 0.952; p=0.023) and gestational age had OR of 01.15 (95%CI 1.11 –18.00; p=0.0350).

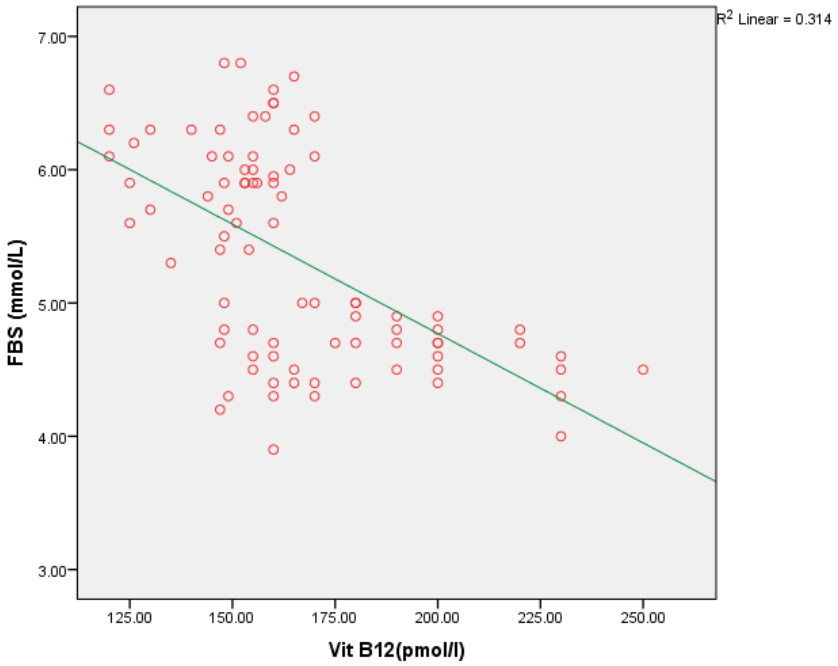

Figure 1: Scattered diagram showing relation between vitamin B-12 status of the patients with FBS level (N=86)

Fasting plasma glucose was significantly negatively correlated with vitamin B12 level in blood (Pearson's r= -0.561, p<0.001).

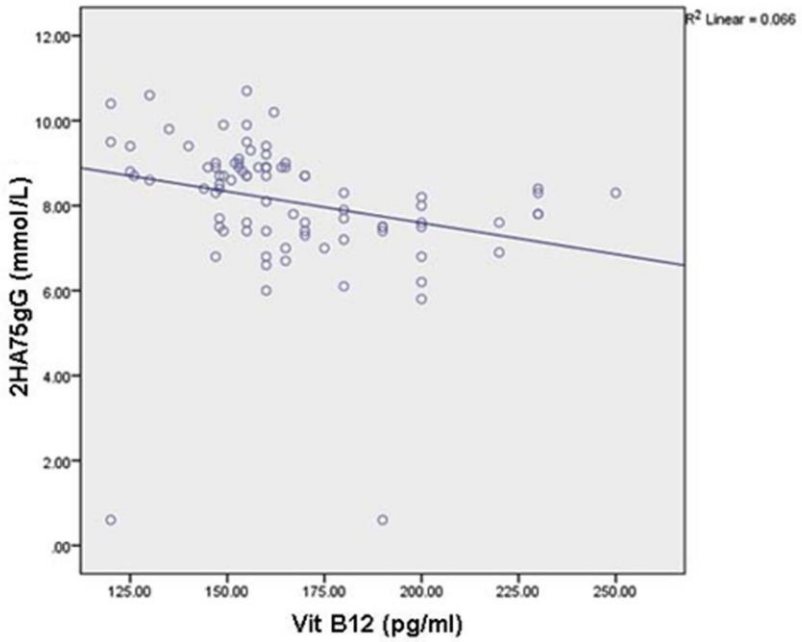

Figure 2: Scattered diagram showing relation between vitamin B-12 status of the patients with 2HA75gmG level (N=86)

Plasma glucose two hours after75gm glucose was significantly negatively correlated with vitamin B12 level in blood (Pearson's r= -0.258, p=0.017).

DISCUSSION

This cross-sectional comparative study was carried out with an aim to estimate the serum vitamin B12 level in pregnant women with GDM and without GDM, compare serum vitamin B12 level between two groups and to evaluate any association between serum vitamin B12 level with GDM. A total of 86 singleton pregnant women between 18-40 years of age in their 29 to 40 weeks of gestation attending antenatal clinic and admitted in the department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib medical university (BSMMU) were included in this study from 211 pregnant women. Among them 43 diagnosed cases of GDM considered as Group A and rest 43 pregnant women without GDM considered as Group B.

In this present study the mean age was 27.00±3.80 years in group A and in group B the mean age was 24.91±4.77 years. Fatema and her colleagues conducted a study in 2017 and their finding is similar to this study. [10] Another study conducted by Natasha and her colleagues found mean age of their Bangladeshi GDM pregnant was 28.35±5.34 years. [11] This study reveals that in group A 33(76.74%) pregnant women were multi gravida. On the contrary, in group B 24(55.81%) pregnant women were multi gravida. Study conducted by Begum et al found that similar findings. [12] Parity is not directly linked to insulin sensitivity deterioration. It is due to progressive ageing and weight gain.

In group A (GDM group) mean weight of the study subjects was 61.84±9.17 kg and in group B (non-GDM) mean weight of the study subjects was 55.24±8.72 kg. In group A maximum 53.50% pregnant women were in 25-29.9 kg/m^2BMI group and in group B maximum 29(67.40%) pregnant women in 18.5-24.9 kg/m^2 BMI group. The mean BMI of the patients in group A was 24.87±3.70 kg/m^2 whereas in group B the mean BMI was 22.39±3.26 kg/m^2. This finding is similar to the finding of Sukumar and associates (Sukumar et al., 2016). Relatively lower sensitivity of insulin in obese patients may be the possible reason for this. [13]

In this study in both group A and B maximum pregnant women had gestational age in between 33-36 weeks. There had no statistically significant difference in mean gestational age (p=0.091) between the groups. In this study the mean gestational age of GDM cases was found 36.16±1.49 weeks. A study conducted by Mustary and colleagues found that mean gestational age of their GDM cases was 36.58 ± 2.34 weeks. Another study conducted by Natasha and Khan found the similar findings. [11]

The percentage of cases having vitamin B-12 level deficiency was statistically significantly more in GDM group than non-GDM group (p=0.031). Among the GDM group 30.23% pregnant women had vitamin B-12 deficiency and among the non-GDM group only 11.63% pregnant women had vitamin B-12 deficiency. The mean vitamin B-12 level was also statistically significantly low in GDM group than non-GDM group (p=0.001). In GDM group the mean vitamin B-12 level was 148.88±13.91 p gm/ml and in non-GDM group the mean was 182.70±27.16 p gm/ml. Study conducted by Sukumar and colleagues found the mean vitamin B-12 level in GDM group was lower than the mean vitamin B-12 level in non-GDM group which is consistent to our findings. [14] Study conducted by Lai and associates shown that the odds of GDM decreased with increased vitamin B12 concentrations, which in turn signified that low vitamin B12 level was significantly associated with high risk of GDM. [15] Another study conducted by Krishnaveni and associates found higher incidence of GDM in vitamin B12 deficient women than non-deficient women. [16] Vitamin B12 deficiency cause impaired methionine and protein synthesis which may prevent lean tissue

deposition and Decrease conversion of methylmalonic acid to succinyl co A, for which vitamin B12 acts as a rate limiting coenzyme, results in the accumulation of methylmalonic acid and may increase lipogenesis and insulin resistance. [17] And insulin resistance cause GDM.

In this present study, it was observed that there was negative significant Pearson's correlation between fasting plasma glucose level with vitamin B12 level (Pearson's r= -0.561. P<0.001). This finding was similar to the findings of the study of Cassinadane and his colleagues. [18] There was also found negative significant Pearson's correlation between plasma glucose level 2HA75gm glucose and vitamin B12 level (Pearson's r=-0.258, P=0.017). This result is similar to the result of the study of Ouzilleau and his colleagues. [19]

It was a cross-sectional study with measures of vitamin B12 at one point of time only. The study was based in one single hospital. However, the women belonged to different religions, socio cultural background and dietary habits that were representative of Bangladeshi population. I found significant statistical difference in vitamin B12 level between women with GDM and normal pregnant women. Although I had identified associations between vitamin B12 and GDM, the study did not prove causation. In future I intend to conduct an interventional study to investigate the risk reduction in GDM with vitamin B12 treatment.

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

CONCLUSION

The present study concluded that serum vitamin B12 level was significantly lower in women with GDM when compare with pregnant women without GDM. Thus, low serum vitamin B12 may be considered as a risk factor for the development of GDM.

RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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The wide range of disciplines involved in association of serum vitamin B12 with gestational diabetes mellitus (GDM) research means that editors need much assistance from references in the evaluation of papers submitted for publication. I would also like to be grateful to my colleagues and family who supported me and offered deep insight into the study.

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