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The Relationship Between Vitamin B12 and Gestational Diabetes in Pregnant Women With and Without Gestational Diabetes Mellitus

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Abstract

Objectives: Studies on the relationship between vitamin B12 and gestational diabetes mellitus (GDM) have shown different results. Given the lack of research in this area in Iran and the inconsistent findings of studies carried out in other nations, this study was conducted in light of the significance of the problem, particularly with regard to the health of expectant mothers.

Materials and Methods: This case-control study was performed on 120 pregnant women referred to Ayatollah Rouhani hospital in Babol, private offices, and health centers to evaluate the vitamin B12 level in women with and without GDM. GDM was defined as 1) after oral ingestion of 75 g glucose, fasting plasma glucose level (PGL) >92 mg/dL, 1-hour PGL >180 mg/dL, or 2-hour PGL >153 mg/dL during 24-28 weeks of gestational age, or 2) in the 100-g oral glucose tolerance test (OGTT), PGL >195 mg/dL, one-hour PGL >180 mg/dL, 2-hour PGL >155, and 3-hour PGL >140, and GDM was diagnosed if there were at least 2 out of 4 mentioned cases. According to the above definition, pregnant women with GDM were placed in the case group, while those without GDM were placed in the control group. After 8 hours of fasting, intravenous blood samples were taken and sent to the laboratory for measurement, and vitamin B12 deficiency was considered <99 pg/dL after 28 gestational weeks.

Results: Vitamin B12 deficiency was prevalent in 14.2% of 120 pregnant women studied. Vitamin B12 deficiency was more common in GDM women than in non-GDM women (58.8%-41.2%). A normal level of vitamin B12 could act as a protective factor against GDM. The vitamin B12 levels increased in the 30- to 40-year-old women with GDM. In other age groups, vitamin B12 levels were higher in non-GDM women than in GDM women. Among 17 women with vitamin B12 deficiency, 52.9% had a fasting PGL >92.

Conclusions: The results of the present study suggest that measuring vitamin B12 levels may aid in the early diagnosis of GDM and prevent maternal and fetal complications.

Keywords: Pregnancy, Gestational diabetes, Vitamin B12

Introduction

Gestational diabetes mellitus (GDM), diagnosed during pregnancy, is a carbohydrate intolerance of varying severity that can cause adverse outcomes for both the fetus and the mother (1,2). Vitamin B12 (cobalamin) is a water-soluble vitamin that plays a key role in DNA methylation and cell metabolism.

Glucose intolerance with variable intensity that is first started or diagnosed during pregnancy is called gestational diabetes (3). Gestational diabetes refers to a condition in which blood glucose levels rise during pregnancy, and symptoms of diabetes are seen in a pregnant woman who has not previously been diagnosed with diabetes (4).

Gestational diabetes occurs when a person is unable to secrete enough insulin to compensate for the nutritional boost during pregnancy, as well as the increased production of fat and anti-insulin hormones produced during pregnancy, such as the human placental hormones prolactin, cortisol, and progesterone. In gestational diabetes, the rate of insulin response per unit of glycemic stimulation (insulinogenic index) is only half that seen in normal pregnancy. Specific stimulus tests have shown increased sensitivity of beta cells to glucose and amino acids in normal pregnancies, while this response is clearly lower in women with gestational diabetes (5,6).

Diabetes increases oxidative stress in the body. Oxidative stress is the result of an imbalance between the production of oxygen-free radicals and the body's antioxidant defense. The association between poor glycemic control and oxidative enhancement has been established. Diabetes increases oxidative stress in various tissues, as evidenced by increased levels of DNA and oxidized proteins and lipids. In addition, diabetes is associated with the stimulation of cellular responses, including activation of

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Key Messages

- The study investigated the relationship between vitamin B12 levels and gestational diabetes mellitus (GDM) in pregnant women. It was found that vitamin B12 deficiency is more prevalent in women with GDM than in those without. The results suggest that maintaining normal vitamin B12 levels may serve as a protective factor against GDM. This study highlights the potential importance of monitoring vitamin B12 levels for early diagnosis and prevention of GDM, emphasizing the need for further research in diverse populations to clarify this relationship.

the protein kinase pathway, increased NF-κB, and stress-related kinases.

The disproportionate activation of these regulatory molecules can also have detrimental effects on cell function, which is effective in the pathogenesis of chronic vascular complications of diabetes.

Some studies have reported that vitamin B12 deficiency can cause insulin resistance and glucose intolerance, leading to GDM, regardless of whether insulin or diet is used to treat the diet or whether it persists after pregnancy (7-9). The prevalence of GDM is >18%, but it is >20% in some Asian countries (10). Vitamin B12 deficiency is common during pregnancy and may affect all fetal and maternal health parameters, such as maternal body mass index (BMI), insulin resistance, and fat profile (11-15). Numerous studies have examined the relationship between the consumption of nutrients, especially carbohydrates and fats, and GDM in pregnant mothers (16). Nevertheless, there is less information about the relationship between micronutrients such as B vitamins and GDM.

It seems that B vitamins, including folate, B6, and B12, may play a role in the pathogenesis of glucose intolerance due to their ability to regulate homocysteine synthesis (17). High concentrations of homocysteine are associated with insulin resistance (18,19). A study in India has shown that there is a relationship between vitamin B12 deficiency and an increased risk of GDM and type 2 diabetes within five years after pregnancy (20). However, several studies on the European population have demonstrated that vitamin B12 levels in GDM women are not significantly different from those in healthy women (21-23). A similar study in the United Kingdom found no relationship between vitamin B12 levels and fasting serum glucose (24). Nevertheless, this relationship was observed in several studies conducted in the UK and India (20,25).

In general, most studies have been carried out in Western societies, but recent evidence suggests that the relationship between vitamin B12 and homocysteine and GDM varies in Asian societies (13,26). Studies on the relationship between vitamin B12 and GDB have represented different results (16,18,19,21,22). Considering that no study has been conducted in this field in Iran, the results of studies performed in other countries have been contradictory. This study was conducted to assess the importance of the issue, especially the health of pregnant mothers.

Due to the presence of oxidative stress and its effect on accelerating the micro- and macrovascular complications of diabetes, the study of how to reduce the body's oxidants and increase the optimal use of synthetic and non-synthetic antioxidants such as vitamin B12 is among the reasons for this study.

Materials and Methods

This case-control study was performed on pregnant women referred to Ayatollah Rouhani Hospital in Babol, private offices, and health centers from March 20, 2020, to March 20, 2021, to evaluate the vitamin B12 level in women with and without GDM.

Initially, the resident implementing the project coordinated with the health deputy; GDM and non-GDM women with gestational weeks of >28 were identified through cooperation and coordination with the Family Health Unit of the corresponding deputy, and the telephone numbers of hospital-affiliated health centers were obtained. We excluded pregnant women with underlying diseases such as hypertension and pernicious anemia. Subsequently, these individuals were invited to participate in this study in collaboration with health centers and family physician bases. The procurement of kits and the collection of samples were coordinated with Pars Private Laboratory.

The sample size was determined to be 60 women in each group, with a confidence level of 95% and a power of 80%, based on the results of a previous study (33) that indicated that vitamin B12 deficiency was 56% in the GDM group and 32% in the control group.

The case group consisted of pregnant women with GDM, which was defined as 1) after oral ingestion of 75 g of glucose, fasting plasma glucose level (PGL) >92 mg/dL, 1-hour PGL >180 mg/dL, or 2-hour PGL >153 mg/dL during 24-28 weeks of gestational age, or 2) in the 100-g oral glucose tolerance test (OGTT), PGL >195 mg/dL, 1-hour PGL >180 mg/dL, 2-hour PGL >155, and 3-hour PGL >140, and GDM was diagnosed if there were at least 2 out of the 4 mentioned cases (3). Women without pregnancy diabetes were allocated to the control group.

First, a pre-designed questionnaire including personal information such as height, weight, age, level of education, residence place, occupation, history of gestational diabetes, and family history was filled in by the physician, and a venous blood sample was taken 8 hours after fasting and sent to Pars Laboratory to measure vitamin B12 levels. Based on the above definition, pregnant women with GDM were in the case group, and pregnant women with no GDM were in the control group. The monobyte reagent from Saman Tajhiz Noor Company was used to measure the vitamin B12 levels of blood samples collected at Pars private laboratory. After 28 gestational weeks, vitamin B12

deficiency was defined as a level of less than 99 pg/dL (4).

Homogenization

The most important factor was the range of age changes. Therefore, efforts were made to ensure that patients were in the same age range to ensure similarity in age between the case and control groups.

After collecting the study data, SPSS was used for statistical analysis. In descriptive statistics, dispersion indices (mean, standard deviation) for quantitative variables, as well as the frequency, percentage, and prevalence for qualitative data, were used to analyze the data. After examining the normality of the data, in the inferential statistics section, the parametric (*t* test and chi-square) and non-parametric (Mann-Whitney) tests were utilized to test the study hypotheses. All data analyses were performed using SPSS 25. A value of $P<0.05$ was statistically considered significant.

Results

In this study, 120 pregnant women referred to Ayatollah Rouhani hospital in Babol, private offices, and health centers were selected using the available sampling method.

The vitamin B12 levels of 60 GDM-pregnant women and 60 pregnant women without GDM were evaluated.

In the study of BMI, it was found that the mean BMI was significantly higher in GDM-pregnant women than in non-GDM pregnant women ($P=0.01$). Although the level of vitamin B12 was higher in pregnant women with GDM, this difference was not statistically significant ($P=0.30$). In the study of gravidity, parity, number of live births, and number of abortions were quantitatively identical, and no significant difference was observed between the two groups (Table 1). In the study of demographic and clinical variables, no significant relationship was found between the two groups, and the two groups were demographically and clinically homogenized (Table 2). In the age group of 30-34, the mean level of vitamin B12 was significantly higher in GDM women ($P=0.01$), and no significant difference was found in other age groups (all *P* values > 0.05) (Table 3). No significant age difference was seen in the level of vitamin B12 between GDM and non-GDM women (All *P* values >0.05) (Table 4). There was no significant difference between vitamin B12 levels and fasting blood glucose (FBS) ($P=0.87$), 1-hour, and 2-hour blood glucose (respectively $P=0.53$ and 0.81) (Table 5). There was no significant difference between vitamin B12 levels and GDM treatment ($P=0.96$) (Table 6).

Table 1. Mean and Standard Deviation of Quantitative Indicators Among Pregnant Women With and Without GDM

Variables	GDM Mean ± SD	Non-GDM M ± SD	*P* Value
BMI (kg/m^2)	31.02±4.84	28.97±4.17	0.01[a]
Age (y)	31.86±6.05	30.18±5.03	0.10[a]
Gravidity	1.87±0.87	1.83±1.09	0.08[a]
Parity	0.98±0.79	0.73±0.95	0.09[a]
Number of live births	0.97±0.78	0.72±0.94	0.11[a]
Number of abortions	0.28±0.84	0.07±0.31	0.16[a]
Vitamin B12 level (pg/dL)	212.58±127.81	183.02±96.02	0.30[b]

[a] Using the t-test; [b] Using the Mann-Whitney test.

Table 2. Relationship Between Studied Variables and Vitamin B12 Levels of Gestational Diabetes Mellitus

Variables	GDM No. (%)	Non-GDM No. (%)	*P* Value[a]
Level of education			0.14
Under Diploma	20 (33.3)	14 (23.3)	
Diploma and associate degrees	22 (36.7)	31 (51.7)	
Bachelor	18 (30.0)	13 (21.7)	
Master's degree and higher	-	2 (3.3)	
Residence place			0.71
Urban	33 (55.0)	31 (51.7)	
Rural	27 (45.0)	29 (48.3)	
Occupation			0.57
Housewife	52 (86.7)	54 (90.0)	
Employed	8 (13.3)	6 (10.0)	

[a] Using the chi-square test.

Table 3. Vitamin B12 Levels in Pregnant Women With and Without GDM by Age

Age (y)	GDM Mean ± SD	Non-GDM Mean ± SD	*P* Value[a]
<20	162.00±132.93	180.33±36.35	0.99
20-24	189.14±96.78	201.42±110.43	0.65
25-29	163.83±87.97	211.83±134.04	0.21
30-34	265.65±160.18	161.15±48.11	0.01
≥35	187.02±98.28	193.50±86.17	0.60

[a] Using the Mann-Whitney test.

Discussion and Conclusion

Given the relatively high prevalence of GDM, especially in developing countries, the lack of identification of maternal and fetal causes and complications, and the fact that researchers still disagree about the risk factors for GDM, this study aimed to examine and compare changes in B12 levels between GDM women and the control group.

The prevalence of vitamin B12 deficiency was 14.2% among 120 studied pregnant women. In the study of Chen et al, the prevalence of vitamin B12 deficiency was 12.9% (27). The prevalence of vitamin B12 deficiency was higher in the current study than in Chen and colleagues' study, which could be due to the differences in lifestyle and food richness in developed countries. The most important finding of the present study was that vitamin B12 deficiency was more common in GDM women than in non-GDM women (58.8 to 41.2%). In other words, the ratio of vitamin B12 deficiency in women with GDM was 1.4 times that in women without GDM. In the study of Sukumar et al, vitamin B12 levels were low in 51.1% of GDM pregnant women. Therefore, there was a relationship

Table 4. Vitamin B12 Levels Between Pregnant Women With and Without GDM Based on Age

Groups	Age (y)	Vitamin B12 (pg/dL)			*P* Value[a]
		≤99 No. (%)	100-129 No. (%)	≥130 No. (%)	
GDM	<20	1 (50)	-	1 (50)	0.33
	20-24	-	2 (28.6)	5 (71.4)	
	25-29	3 (25)	1 (8.3)	8 (66.7)	
	30-34	1 (5.9)	3 (17.6)	13 (76.5)	
	≥35	3 (13.6)	1 (4.5)	18 (81.8)	
Non-GDM	<20	-	-	3 (100)	0.60
	20-24	2 (16.7)	1 (8.3)	9 (75)	
	25-29	4 (22.2)	1 (5.6)	13 (72.2)	
	30-34	1 (5)	7 (35)	12 (60)	
	≥35	1 (14.3)	1 (14.3)	5 (71.4)	

[a] Using the chi-square test.

Table 5. Relationship Between Vitamin B12 Levels and Blood Glucose

Glucose (mg/dL)	Vitamin B12 (pg/dL)			*P* Value[a]
	≤99 No. (%)	100-129 No. (%)	≥130 No. (%)	
FBS				
≤92	8 (13.1)	10 (16.4)	43 (70.5)	0.87
>92	9 (15.3)	8 (13.6)	42 (71.2)	
1-hour blood glucose				
≤180	16 (13.7)	18 (15.4)	3 (70.9)	0.53
>180	1 (33.3)	-	2 (66.7)	
1-hour blood glucose				
≤153	17 (14.3)	18 (15.1)	84 (70.6)	0.81
>153	-	-	1 (100)	

[a] Using the chi-square test.

Table 6. Relationship Between Vitamin B12 Levels and Treatment Type of Gestational Diabetes Mellitus

Glucose (mg/dL)	Vitamin B12 (pg/dL)			*P* Value[a]
	≤99 No. (%)	100-129 No. (%)	≥130 No. (%)	
Treatment				
Diet	6(15.8)	5(13.2)	27(71.1)	0.96
Insulin	4(18.2)	3(13.6)	15(68.2)	

[a] Using the chi-square test.

between vitamin B12 deficiency and GDM (25). Wang et al reported that the concentrations of pooled serum vitamin B12 were significantly lower in the GDM group than in the non-GDM group (28), which is consistent with the present study. In a similar study, Saravanan et al found that low B12 levels in early pregnancy were associated with a higher risk of GDM. They have stated that generalizing these results requires further studies on the effect of early pregnancy on B12 levels and subsequent hyperglycemia (29). In a 2020 study, Liu et al reported that a reduced risk of diabetes is associated with higher or normal levels of vitamin B12. They have explained that further studies with a large sample size from different regions around the world are needed to strengthen the current evidence (30). Kouroglou et al, in a meta-analysis study, found that there was a significant relationship between vitamin B12 deficiency and GDM. Still, no statistically significant difference was detected in the other four studies (31). Guven et al suggested no difference in vitamin B12 levels between the GDM and non-GDM groups (21). Based on the available studies and the results of this study, the relationship between vitamin B12 levels during pregnancy and the risk of GDM is unclear and still contradictory.

This is one of the few studies on vitamin B12 changes in GDM. To our best knowledge, no comparable research has been conducted in Iran, so this is the first study to investigate the role of vitamin B12 in GDM.

The present study investigated the role of vitamin B12 and concluded that normal levels of vitamin B12 could act as a protective factor against GDM. Of course, this relationship was not statistically significant, but it was a clinically important finding. Although the low number of cases with vitamin B12 deficiency can be explained to justify this finding, it is possible that as the number of cases with vitamin B12 deficiency increases, the protective role of vitamin B12 becomes significant.

In a study by Maher et al, it was concluded that vitamin B12 deficiency was associated with insulin resistance. They identified a potential method to reduce GDM risk by enhancing maternal metabolic health through the use of vitamin B12 supplements (5). According to the results of Xie et al, vitamin B12 was significantly related to GDM risk (6). Moreover, Li et al illustrated that vitamin B12 deficiency increased GDM by 1.12 times (32).

One of the strengths of this study is its examination of the relationship between vitamin B12 levels and GDM using demographic variables, as vitamin B12 levels are dependent upon individual characteristics, regardless of pregnancy. One of the significant results of this study was the increase in vitamin B12 levels in 30- to 40-year-old women with GDM. In other age groups, vitamin B12 levels were higher in GDM women than in non-GDM women. The results obtained are so new that they cannot be justified. Still, this finding could pave the way for future studies on the relationship between vitamin B12 and the factors that reduce or increase it during pregnancy. Regarding other variables such as BMI, treatment type, gravidity, parity, number of live births, and number of abortions and their relationship with vitamin B12, no significant findings were achieved; hence, the ongoing study refrained from expressing them again. Another finding of the current research was related to the study of vitamin B12 levels and the number of cases that were considered to have GDM based on fasting blood glucose and 1- and 2-hour blood glucose. Overall, in the present study, 59 women had a fasting PGL >92. Three pregnant women had a 1-hour PGL >180, and two of them (3

women) had a fasting PGL >92 at the same time. One woman had a 2-hour PGL >153, which overlapped with a fasting PGL >92. The results showed that among 17 women with vitamin B12 deficiency, 52.9% had a fasting PGL >92, indicating that vitamin B12 deficiency might be associated with GDM in a large sample size. Krishnaveni et al found a relationship between vitamin B12 deficiency and GDM in both GDM and non-GDM women, and they recommended further studies (20). Idzior-Waluś et al. stated that there was a significant relationship between vitamin B12 deficiency and GDM, too (22).

Based on the results of the current study, measuring vitamin B12 levels might help with the early diagnosis of GDM and prevent maternal and fetal complications.

Authors' Contribution

Conceptualization: Leyla Oladighdikolaei, Parvin Sajadi Kaboudi, Mahmoud Hajiahmadi, Zinatosaadat Bouzari, Seyedeh Zahra Bouzari.
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Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Babol University of Medical Sciences with code IR.MUBABOL.REC.1399.324.

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