

## RELATIONSHIP OF MATERNAL VITAMIN B12 STATUS IN PREGNANCY WITH PRETERM BIRTH AND MATERNAL HEALTH RISKS

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**Vitamin B12 deficiency is associated with obesity and overweight, anemia and possible uterus and fetus neurological impairments. This study was aimed to reveal a health risk for pregnant women with vitamin B12 deficiency, as well as the preterm birth one. The findings demonstrated no strong correlation between serum vitamin B12 level and preterm birth risk. But an inverse association between vitamin B12 level and overweight before pregnancy as well as when giving birth was found. There was confirmed the noteworthy connection between meat consumption and vitamin B12 level, as well a correlation between the vitamin B12 level and that of hemoglobin in pregnant women was found. The need in further investigation was emphasized to increase the reproducibility of results.**

*Key words: vitamin B12, preterm birth, pregnancy, overweight, hemoglobin.*

Preterm birth and low birth weight cause more than 2.9 million annual neonatal deaths worldwide [1]. Consequently, an effort should be made to prevent such cases to reduce the number of children deaths. Prevention is not always easy as the preterm birth and low birth weight have a complicated and sometimes unknown etiology [2]. Complications of prematurity include respiratory distress syndrome, brain hemorrhage, jaundice, infections, bronchopulmonary dysplasia, etc. [3, 4]. The preterm birth is believed to be a syndrome with a numerous potentially independent reasons, resulting in many studies discussing the role of vitamin deficiencies as a probable cause for preterm birth and low birth weight [5–8].

Vitamin B12, also known as cobalamin, plays a major role in the DNA synthesis and methylation [9, 10]. It is also important for the energy production of a cell [11]. Vitamin B12 mutually with folic acid is a cofactor for the conversion of homocysteine to methionine, an important methyl donor required for the synthesis of neurotransmitters and phospholipids [12]. Low vitamin B12 concentrations during pregnancy may affect the placental growth [13], as well as normal development of infant brain [14]. Suboptimal level of vitamin B12 has been shown to be associated with low birth weight and an adverse lipid profile in neonates [15].

The aim of our study was: 1) to compare the obstetrics anamnesis between the women who gave birth on term and those delivered prematurely, 2) to reveal the prevalence of vitamin B12 insufficiency in pregnancy, 3) to determine its association with preterm birth and low birth weight, 4) to examine

its association with spontaneous abortions, and 5) to investigate its relationship with obesity and hemoglobin levels in pregnant women.

**Study design.** This is a retrospective and prospective case-control study using the data obtained from the women whose pregnancy was monitored at the outpatient Clinic of the University Hospital of Obstetrics and Gynecology «Maichin dom», Sofia, Bulgaria. The collected data comprise the maternal weight and BMI before pregnancy as well as at the time of giving birth, obstetrics history, serum levels of vitamin B12 and hemoglobin, information about meat consumption.

**Cases.** Study cases were 107 women who gave birth before the 37<sup>th</sup> week of gestation.

**Controls.** Study controls were 101 women who gave birth after the 37<sup>th</sup> week of gestation.

**Data collection.** Information was collected on women's age, height, weight, parity, miscarriages, and meat consumption at their first visit to the clinic. Weight and height were obtained under standardized conditions and used to calculate BMI. Second measurement of weight and height was performed almost before birth and BMI was calculated again. Gestational age was calculated starting from the first day of the last menstruation.

Blood samples were collected from each patient by venipuncture and collected into vacutainer heparine tubes. Hemoglobin measurement was automatically analyzed. Plasma vitamin B12 was measured in 12–14 week of gestation by either the electrochemiluminescence or immunochemical method. We considered three groups depending on the level of vitamin

B12: 1) Deficiency, i. e. with the plasma concentrations of vitamin B12 < 148 pmol/L; 2) Subclinical deficiency, i. e. with the plasma concentrations of vitamin B12 148–220 pmol/L; and 3) Normal level, i. e. with the plasma concentrations of vitamin B12 > 220 pmol/L.

**Statistical analysis.** Quantitative variables are presented as mean values (arithmetic mean and median), standard deviations, minimum and maximum values. Variables are presented by (*n*) and relative (%) capabilities. The listed distributions of the quantitative variables are evaluated with a Kolmogorov – Smirnov test (one-sample Kolmogorov – Smirnov test). Normal distribution of quantitative variables into two independent groups were comparatively analyzed with *t*-test (Independent-Samples *t*-test), and if the distribution was not normal, Mann – Whitney test was used. The relationship between two category variables was examined with a Chi-Square Test. Statistical significance is assumed at *p* < 0.05. The specialized Statistical Package for the Social Sciences (SPSS) version 19.0 was used to process the survey data.

**Results.** We started our investigation by comparing the two groups on their age, weight and BMI to look for the preterm birth feature. The table below (Table 1) shows the difference in the mean gestational week of giving birth, i. e. 30.85±3.86 for cases and 38.66±1.53 for the controls. We found no difference in the mean age for both groups. As for the weight and BMI before pregnancy and at birth the results demonstrate them all higher in the group of the controls.

We used Fisher's Exact Test to assess the number of pregnancies and spontaneous abortions among the two groups of patients (Table 2 and 3). We found a significant difference (*p* < 0.001) in the number of pregnancies between the cases and controls. The current pregnancy was first for 48.6% (*n* = 52) of

cases and 76% (*n* = 76) of the controls, as well as it was the second for 34.6% (*n* = 37) of cases and 20% (*n* = 20) of the controls. In 89.7% (*n* = 96) of cases there was no report on a spontaneous abortion in the past. This was stated in 91.1% (*n* = 92) of the controls.

To find a correlation between the parameters discussed in Table 1 and the level of vitamin B12 we divided each of two groups into three subgroups, i.e. with the level of vitamin B12 < 148 pmol/L, 148–220 pmol/L, and > 220 pmol/L. We found no significant difference in weight and BMI between the cases in three groups (Table 4). However, such a difference was revealed in the controls (Table 5).

The weight of the control group of women with vitamin B12 level < 148 pmol/L at the time they gave birth was 96.73±15.56 kg and of those with level > 220 pmol/L was 80.23±12.62 kg (*p* = 0.01). BMI before pregnancy in the control group of women with vitamin B12 level < 148 pmol/L was 32.5±6.5, while in women with vitamin B12 level > 220 pmol/L it was 25.25±3.34 (*p* = 0.004). This tendency is similar when observing the BMI at the time those women gave birth. It was 37.11±6.52 in women with vitamin B12 level < 148 pmol/L and 29±4.62 in the women with vitamin B12 level > 220 pmol/L (*p* = 0.001).

When obtaining these results, we decided to combine the cases and controls, and hence to divide the patients only according to their vitamin B12 serum level. Thereby we may see more clearly the correlation between vitamin B12 concentration in the blood and the aforementioned parameters. We compared the patients with different level of vitamin B12: 1) with vitamin B12 concentration < 148 pmol/L and 148–220 pmol/L; 2) with vitamin B12 concentration < 148 pmol/L and > 220 pmol/L; and 3) with vitamin B12 concentration 148–220 pmol/L and > 220 pmol/L (Table 6). We found a strong difference between the cohort with low

Table 1

**Maternal age, weight and BMI before pregnancy and at birth, gestational week at birth in the group of cases and controls**

Parameter	Group	<i>n</i>	Mean	SD	Min	Max
Age	Controls	101	29.49	4.58	19.00	40.00
	Cases	107	29.39	5.12	17.00	42.00
Weight before pregnancy	Controls	101	72.38	12.80	45.00	125.00
	Cases	107	63.11	11.66	42.00	88.00
Weight at birth	Controls	101	82.20	16.50	3.00	130.00
	Cases	107	74.98	12.64	53.00	106.00
BMI before pregnancy	Controls	101	26.42	4.95	15.57	45.91
	Cases	107	22.79	4.67	15.78	38.22
BMI at birth	Controls	101	30.02	6.38	1.05	48.04
	Cases	107	27.05	4.88	19.36	41.33
Week of giving birth	Controls	101	38.66	1.53	34.00	42.00
	Cases	105	30.85	3.86	1.00	38.00

Table 2

**Parity of cases and controls**

Current pregnancy	Controls		Cases		Total		p
	n	%	n	%	n	%	
1	76	76.0	52	48.6	128	61.8	<0.001
2	20	20.0	37	34.6	57	27.5	
3	2	2.0	14	13.1	16	7.7	
4	2	2.0	4	3.7	6	2.9	

Table 3

**Parity of cases and controls**

Spontaneous abortions	Controls		Cases		Total		p
	n	%	n	%	n	%	
0	92	91.1	96	89.7	188	90.4	<0.166
1	9	8.9	7	6.5	16	7.7	
2	0	0.0	4	3.7	4	1.9	

Table 4

**Correlation between serum vitamin B12 level and weight as well as BMI of cases**

Group	Parameter	Vit. B12 level	n	Mean	SD	Min	Max	p
Cases	Weight before pregnancy	< 148 pmol/L	39	61.74	13.51	42.00	88.00	0,642
		148–220 pmol/L	20	64.40	11.47	47.00	86.00	
		> 220 pmol/L	48	63.69	10.16	42.00	86.00	
	Weight at birth	< 148 pmol/L	39	73.87	14.35	53.00	106.00	0,789
		148–220 pmol/L	20	75.40	12.90	57.00	101.00	
		> 220 pmol/L	48	75.71	11.17	53.00	93.00	
	BMI before pregnancy	< 148 pmol/L	39	22.22	4.74	15.78	31.93	0,584
		148–220 pmol/L	20	23.49	4.37	17.47	30.85	
		> 220 pmol/L	48	22.96	4.78	17.26	38.22	
BMI at birth	< 148 pmol/L	39	26.61	5.04	19.36	38.47	0,770	
	148–220 pmol/L	20	27.45	4.55	21.19	35.79		
	> 220 pmol/L	48	27.25	4.95	19.47	41.33		

Table 5

**Correlation between serum vitamin B12 level and weight as well as BMI of controls**

Group	Parameter	Vit. B12 level	N	Mean	SD	Min	Max	p
Controls	Weight before pregnancy	< 148 pmol/L	11	84.82	16.77	60.00	105.00	0.024
		148–220 pmol/L	12	77.17	20.30	56.00	125.00	
		> 220 pmol/L	78	69.88	9.23	45.00	106.00	
	Weight at birth	< 148 pmol/L	11	96.73	15.56	73.00	120.00	0.01
		148–220 pmol/L	12	81.67	30.05	3.00	130.00	
		> 220 pmol/L	78	80.23	12.62	3.00	108.00	
	BMI before pregnancy	< 148 pmol/L	11	32.50	6.50	22.04	41.12	0.004
		148–220 pmol/L	12	28.45	7.43	21.22	45.91	
		> 220 pmol/L	78	25.25	3.34	15.57	36.68	
BMI at birth	< 148 pmol/L	11	37.11	6.52	26.81	48.04	0.001	
	148–220 pmol/L	12	30.14	11.14	1.10	47.75		
	> 220 pmol/L	78	29.00	4.62	1.05	37.37		

levels of vitamin B12 and that with normal level of vitamin B12 when comparing the weight before pregnancy ( $p = 0.006$ ), weight at the time they gave birth (0.002), BMI before pregnancy ( $p = 0.001$ ) and BMI at time they gave birth ( $< 0.001$ ).

Since vitamin B12 is found in animal-derived foods only and it is vital for the body formation, we investigated its levels in the cases and controls as

we divided them according to whether they consume meat products regularly or irregularly (Table 7). We found a significant difference in the level of vitamin B12 in case of regular meat consumption in both the cases and controls ( $p < 0.001$ ). In 89.7% ( $n = 35$ ) of cases and 90.9% ( $n = 10$ ) of the controls those, irregularly consuming meat, had low level of vitamin B12. On the other hand, 95.8% ( $n = 46$ )

Table 6

**Comparison between cohorts with different levels of vitamin B12, weight and BMI before pregnancy and at the time of giving birth**

Parameter	Groups compared		
	< 148 pmol/L	< 148 pmol/L	148–220 pmol/L
	148–220 pmol/L	> 220 pmol/L	> 220 pmol/L
	<i>p</i>	<i>p</i>	<i>p</i>
Weight before pregnancy	0.156	0.006	0.548
Weight at birth	0.079	0.002	0.528
BMI before pregnancy	0.124	0.001	0.270
BMI at birth	0.052	<0.001	0.310

Table 7

**Correlation between regular meat consumption and vitamin B12 level**

Group	Mean consumption	Vitamin B12 level						Total		<i>p</i>
		< 148 pmol/L		148–220 pmol/L		> 220 pmol/L		<i>n</i>	%	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%			
Controls	regularly	1	9.1	3	25.0	71	91.0	75	74.3	< 0.001
	irregularly	10	90.9	9	75.0	7	9.0	26	25.7	
Cases	regularly	4	10.3	9	45.0	46	95.8	59	55.1	< 0.001
	irregularly	35	89.7	11	55.0	2	4.2	48	44.9	
Total	regularly	5	10.0	12	37.5	117	92.9	134	64.4	< 0.001
	irregularly	45	90.0	20	62.5	9	7.1	74	35.6	

Table 8

**Correlation between vitamin B12 level and spontaneous abortions**

Group	Spontaneous abortions	Vitamin B12 level						Total		<i>p</i>
		< 148 pmol/L		148–220 pmol/L		> 220 pmol/L		<i>n</i>	%	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%			
Controls	0	10	90.9	11	91.7	71	91.0	92	91.1	1.000
	1	1	9.1	1	8.3	7	9.0	9	8.9	
Cases	0	36	92.3	19	95.0	41	85.4	96	89.7	0.603
	1	2	5.1	0	0.0	5	10.4	7	6.5	
Total	2	1	2.6	1	5.0	2	4.2	4	3.7	0.675
	0	46	92.0	30	93.8	112	88.9	188	90.4	
	1	3	6.0	1	3.1	12	9.5	16	7.7	
	2	1	2.0	1	3.1	2	1.6	4	1.9	

of cases and 91% ( $n = 71$ ) of the controls who had been consuming meat regularly had a normal level of vitamin B12.

Our team tried to find a correlation between low serum vitamin B12 concentration and the incidence of miscarriages (Table 8). We did not note such a relationship. In the group of cases with vitamin B12 level < 148 pmol/L 5.1% ( $n = 2$ ) had one miscarriage and 2.6% ( $n = 1$ ) had two miscarriages. In the group of controls with vitamin B12 level < 148 pmol/L 9.1% ( $n = 1$ ) had one miscarriage.

When searching a correlation between vitamin B12 concentration and blood hemoglobin level we combined the two groups and divided them only according to the level of the vitamin (Table 9). We found a significant difference in the hemoglobin level depending on vitamin B12 concentration ( $p = 0.038$ ). The mean hemoglobin level for the women with vitamin B12 concentration < 148 pmol/L was  $111.10 \pm 11.02$ , in those with vitamin B12 concentration of 148–220 pmol/L it was  $115.19 \pm 11.41$ , and in the ones with vitamin B12 concentration > 220 pmol/L it made  $115.97 \pm 11.31$ .

Table 9

Correlation between vitamin B12 and hemoglobin levels

Vitamin B12	n	Hemoglobin					F	dfs	p
		Mean	Median	SD	Min	Max			
< 148 pmol/L	49	111.10	112.00	11.02	70.00	136.00	3.33	2.204	0.038
148–220 pmol/L	32	115.19	114.00	11.41	97.00	145.00			
> 220 pmol/L	126	115.97	115.00	11.31	90.00	153.00			

Table 10

Comparison between cohorts with different levels of vitamin B12 and hemoglobin level

Parameter	Compared groups		
	< 148 pmol/L	< 148 pmol/L	148–220 pmol/L
	148–220 pmol/L	> 220 pmol/L	> 220 pmol/L
	p	p	p
Hemoglobin	0.249	0.029	0.935

Table 11

Correlation between vitamin B12 serum concentration and week of gestation when giving birth

Group	Vitamin B12 level	n	Mean	Median	SD	Min	Max	p
Controls	< 148 pmol/l	11	38.64	39.00	2.16	34.00	42.00	0.677
	148–220 pmol/l	12	38.42	38.00	1.24	37.00	41.00	
	> 220 pmol/l	78	38.71	39.00	1.49	35.00	42.00	
Cases	< 148 pmol/l	39	31.00	32.00	2.52	26.00	35.00	0,323
	148–220 pmol/l	19	30.32	32.00	2.75	26.00	34.00	
	> 220 pmol/l	47	30.94	32.00	5.04	1.00	38.00	

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To elucidate the relation between vitamin B12 concentration and the level of hemoglobin we compared the cohorts with different level of vitamin B12 as we have done with other parameters (Table 10). The groups we compared were as follows: 1) with vitamin B12 concentration < 148 pmol/L and 148–220 pmol/L; 2) with vitamin B12 concentration < 148 pmol/L and > 220 pmol/L; and 3) with vitamin B12 concentration 148–220 pmol/L and > 220 pmol/L. A significant difference was found in the second group which shows that the most prominent change in hemoglobin level was in the women with low level of vitamin B12 and those with normal one ( $p = 0.029$ ).

Our main aim in this study was to look for a correlation between the deficit of vitamin B12 and the preterm birth (Table 11). Since the published data concerning the effect of vitamin B12 concentration is controversial, we made same calculations as for the possible risks of low level of the vitamin during pregnancy. Even though we found significant alterations in some of our tests, we could not establish an association between the serum level of vitamin B12 in pregnant women and the risk of preterm birth.

**Discussion**

Numerous studies confirm that lower maternal B12 levels are associated with an increased risk of

preterm birth [15]. The relevantly high prevalence of preterm birth (5–18% of pregnancies) and its various causes makes essential the solving of this problem for the sake of health of future generations [16–19]. The consequences for the premature newborns may lead to serious short and long-term health problems [3, 20]. However, current evidence for such a correlation is still controversial. Taking this into consideration, we divided our patients depending on the week of gestation they gave birth, and measured serum concentration of vitamin B12. Our results showed no significant relation between vitamin B12 blood level and the risk of preterm birth. We registered vitamin B12 insufficiency in 23 of the controls and in 58 of the cases. On the other hand, normal vitamin B12 level was registered in 78 of the controls and in 47 of cases. Even though, there is no statistical significance, the difference in the numbers is obvious and more studies with much larger cohorts are needed.

Our investigation demonstrated interesting findings regarding the weight and the BMI of the women before pregnancy and at the time they gave birth depending on their vitamin B12 level in blood. We found that correlation in the group of controls – those with low level of vitamin B12 had mean BMI at the time they gave birth of  $37.11 \pm 6.52 \text{ kg/m}^2$  and

body weight of  $96.73 \pm 15.56$  kg, while those with normal level of vitamin B12 had mean BMI at the time they gave birth of  $29 \pm 4.52$  kg/m<sup>2</sup> and body weight of  $80.23 \pm 12.62$  kg. The same is observed for the BMI and body weight before pregnancy. In the group of the women with low level of vitamin B12 the mean BMI was  $32.5 \pm 6.5$  kg/m<sup>2</sup> and their mean body weight was  $84.82 \pm 16.77$  kg. These results were  $25.25 \pm 3.34$  kg/m<sup>2</sup> and  $69.88 \pm 9.23$  kg, correspondingly, for the women with normal level of vitamin B12. This demonstrates the probable inverse association of vitamin B12 levels and obesity, as previously reported [21]. Remarkably, this was detected before pregnancy and at term which shows even stronger correlation between these two parameters. Further investigation is needed to understand the underlying mechanisms.

The animal products are well known to be a source of vitamin B12, especially meat. Measuring the vitamin concentration in women, consuming and not consuming meat, we managed to find a significant link between the meat consumption and vitamin B12 level. This was detected in the group of cases as well as that of the controls. Our results emphasize the need of appropriate meat consumption in young women. We should certainly take into consideration some religious and social concerns regarding the meat eating. In that case, the physicians need to explain all the risks following vegetarian or nearly vegetarian diet. Moreover, vitamin B12 level should be measured regularly and should be supplemented when needed.

Another correlation we found concerning the level of vitamin B12 is that with hemoglobin level. Pregnant women are a risk group for iron-deficiency anemia due to combination of the factors such as decreased iron supply, the iron requirements of the growing fetus, and expansion of maternal plasma volume [22]. Low vitamin B12 le-

vels are also reported to cause iron-deficiency anemia [23]. We detected a mean hemoglobin level of  $111.1 \pm 11.02$  in pregnant women with vitamin B12 level of  $< 148$  pmol/L,  $115.19 \pm 11.41$  in pregnant women with vitamin B12 level of  $148-220$  pmol/L, and  $115.97 \pm 11.31$  in pregnant women with vitamin B12 level of  $> 220$  pmol/L. Consequently, the hemoglobin level decreases with the decreasing of vitamin B12 concentration. Low hemoglobin is an independent risk factor for poor intrauterine growth and increased risk of preterm births, low birth weight. The combination with the impairments of low vitamin B12 level may lead to serious consequences for both the mother and fetus.

### Conclusion

Vitamin B12 is vital for cell growth and population during pregnancy. Deficiency of the vitamin occurs most likely in the women with inadequate diets. The impact of low vitamin B12 level is widely discussed in literature and a vast variety of health conditions are associated with it. Our study revealed a correlation between maternal vitamin B12 deficiency, overweight and low hemoglobin level. Even though, many profound reports disclose an association between vitamin B12 low concentration and preterm birth, we could not find any. However, this evidences that such correlation is still controversial. Further studies may evaluate the correlation between vitamin B12 and preterm birth, as well as may help in better understanding the impact of vitamin B12 over pregnant women.

### Conflict of interests

Authors declare no conflict of interests.

### Acknowledgements

We express our gratitude to Mr. T. Kundurdgiev for the statistical support.

Национална научна програма «Млади учени и постдокторанти».

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### **ЗВ'ЯЗОК МІЖ РІВНЕМ ВІТАМІНУ В12 ПІД ЧАС ВАГІТНОСТІ ТА ПЕРЕДЧАСНИМИ ПОЛОГАМИ Й РИЗИКАМИ ДЛЯ ЗДОРОВ'Я МАТЕРІ**

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**Дефіцит вітаміну В12 пов'язаний із ожирінням та надмірною вагою, анемією та можливими неврологічними порушеннями матки та плода. Метою дослідження було виявлення ризиків для здоров'я вагітних із дефіцитом вітаміну В12 та передчасних пологів. Отримані результати не підтвердили наявності значної кореляції між рівнем вітаміну В12 у сироватці крові вагітних та ризиком передчасних пологів. Проте виявлено зворотний зв'язок між рівнем вітаміну В12 і надмірною вагою до вагітності і під час пологів. Підтверджено значний зв'язок між споживанням м'яса й рівнем вітаміну В12, виявлено кореляцію між рівнями вітаміну В12 й гемоглобіну у вагітних. Підкреслено необхідність проведення подальших досліджень для підвищення відтворюваності результатів.**

*Ключові слова:* вітамін В12, передчасні пологи, вагітність, надмірна вага, гемоглобін.

Accepted in 17.04.2020