Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(1): 121-124
doi: 10.52142/omujecm.39.1.24

The effects of vitamin deficiencies in the first trimester on pregnancy outcomes

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Received: 22.08.2021 • **Accepted/Published Online:** 22.09.2021 • **Final Version:** 01.01.2022

Abstract

Adequate maternal nutrition is crucial for pregnancy and fetal growth, and thereby influences pregnancy outcome. In this study, we investigate the relationship between certain vitamin levels of first trimester pregnancy and its maternal-fetal outcomes. This retrospective study was conducted between January 2020 and July 2020 by evaluating data drawn from the hospital database. Serum vitamin B12, 25OH-vitamin D, folic acid and ferritin levels were evaluated in 499 women during the first trimester of pregnancy and confounding factors were analyzed. The mean age was 27 years. The mean birth weight of newborn was 3300g. The vaginal delivery rate was 73.1% whereas caesarean delivery rate was 26.9%. Neonatal intensive care unit (NICU) was needed in 8% of newborns. Meconium was seen in 12.6% of newborns. There was a significant statistical difference between caesarean section and vaginal delivery group with respect to 25OH-vitamin D, vitamin B12, and folic acid levels($p<0.001$). All three vitamins were low in first trimester in caesarean delivery group. In contrast, ferritin levels were similar between two groups. 25OH-vitamin D, folic acid and vitamin B12 levels were significantly low in the presence of meconium($p<0.001$) whereas the level of ferritin was significantly high in the presence of meconium($p=.0.001$). 25 OH-vitamin D ($p=0.001$), vitamin B12 ($p<0.001$) and ferritin($p<0.001$) levels were significantly low in mothers of newborns hospitalized in NICU. In contrast, folic acid level was similar between two groups($p=0.066$). Adequate levels of certain vitamins in the first trimester of pregnancy are crucial for a healthy pregnancy and newborn.

Keywords: ferritin, folic acid, 25-OH vitamin D, pregnancy outcome, vitamin B12

1. Introduction

Vitamins are essential for growth and functions of the body. Therefore, it is crucial to supply vitamin deficiencies in pregnancy to decrease unwanted perinatal outcomes. There is a physiological hemodilution in pregnancy leading to decrease in plasma levels of some vitamins whereas others are not affected due to increased carrier proteins (1). Folate has an important role in the prevention on neural tube defects (NTDs). Also, epigenetic patterns and the phenotype of the offspring are affected from the maternal folate status (2). Vitamin B_{12} is also a co-factor of enzymes catalyzing reactions essential for growth and development (3). Ferritin is a kind of intracellular protein showing the iron stores of the body (4). A low level of serum ferritin is used as a parameter of iron deficiency anemia which is very common in pregnancy. Vitamin D including cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) is a precursor of hormones which are important in the regulation of calcium and phosphate metabolism (5). Higher requirement for vitamins during pregnancy makes women prone to vitamin deficiency therefore inadequate supply exhausts the body stores of pregnant women. Optimal vitamin supply is important during early pregnancy as it influences the future health and wellbeing of the fetus. Because of this, vitamin deficiency in pregnancy is a public health problem. In this study, we investigate the relationship between vitamin B_{12}, folic acid, ferritin, and vitamin D25(OH) levels of first trimester pregnancy and its maternal-fetal outcomes.

2. Materials and Methods

This retrospective study was conducted between January 2020 and July 2020 by evaluating data drawn from the hospital database of patients who underwent routine antenatal visit at Samsun Research and Training Hospital. This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of GOKA/2021/10/2. Informed consent was obtained from all individual participants included in the study. The eligibility criteria for study enrollment were: 1) pregnancy ≥ 37wk 2) age 18–45 years;3) without previous history of chronic illnesses (diabetes mellitus, thyroid problems, hypertension, autoimmune diseases); 4) without

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previous caesarean section history; 5) no alcohol or drug abuse; 6) singleton viable pregnancy. Serum vitamin B_{12}, 25OH-vitamin D, folic acid and ferritin levels were evaluated in 499 women during the first trimester of pregnancy and confounding factors were analyzed. Age, gravida, parity, birth weight, delivery by vaginal or caesarian section, neonatal intensive care unit (NICU) demand, apgar scores (0. and 5. min) and presence of meconium were recorded. Electrochemiluminescence immunoassay (ECLIA) was used for measurements of Vitamin B_{12}, folate and ferritin levels. High performance liquid chromatography (HPLC) was used for measurements of 25OH-vitamin D levels. Gestational age was calculated according to the last menstrual period and also confirmed by ultrasonography in all women. Descriptive statistics results will be given as mean ± standard deviation or median (min-max) for numerical variables and number and/or percentage of patients for categorical variables. All continuous data are expressed as mean ± standard deviation. The comparative analysis is made with the Mann-Whitney U test for continuous data and $\chi 2$ test for categorical data. The ratio of categorical variables will be compared between groups using the chi-square test. P <0.05 will be considered statistically significant. Patients with missing information or data on file were excluded from the study. SPSS statistical software for Windows (Statistical Package for Social Sciences, version 16.0, SPSS Inc. Chicago, Illinois, USA) was used to evaluate the study results.

3. Results

We enrolled a total of 499 pregnant women in this study. Demographic characteristics and pregnancy results are described in Table 1. The mean age was 27 years. The mean gravida and parity were 2 and 1 respectively. The mean birth weight of newborn was 3300g. The mean Apgar scores were 9 and 10 at 0 and 5 minutes respectively. The vaginal delivery rate was 73.1% whereas cesarean delivery rate was 26.9%. Neonatal intensive care unit (NICU) was needed in 8% of newborns. Meconium was seen in 12.6% of newborns.

Table 1. Demographic characteristics and pregnancy results

	Patients (n=499)
Age (y)	27 (18-46) [a]
Gravida (n)	2 (1-3) [a]
Parity (n)	1 (0-2) [a]
Birthweight of newborn (g)	3300 (1780-4900) [a]
Apgar scores	
0. min	9 (5-9) [a]
5. min	10 (6-10) [a]
Delivery	
Vaginal (%)	365 (% 73.1) [b]
Caesarean section (%)	134 (% 26.9) [b]
NICU demand	
No (%)	459 (% 92) [b]
Yes (%)	40 (% 8) [b]
Meconium presence	
No (%)	436 (% 87.4) [b]
Yes (%)	63 (% 12.6) [b]

a: median (min-max), b: n (%), y:year, g:gram

The vitamin levels of women were presented in Table 2. Mean 25OH-vitamin D level was 9 ng/ml, vitamin B_{12} was 177pg/ml, ferritin 11ng/ml and folic acid was 5.64 ng/ml respectively.

Table 2. The vitamin levels in first trimester

	Patient (n=499)
25OH-vitamin D (ng/ml)	9 (2-44)
Vitamin B_{12}(pg/ml)	177 (44-890)
Ferritin (ng/ml)	11 (1.53-344)
Folic Acid(ng/ml)	5.64 (1.11-28)

We compared the way of delivery and serum vitamin levels in Table 3. There was a significant statistical difference between caeserian section and vaginal delivery patients with respect to 25OH-vitamin D, vitamin B_{12}, and folic acid levels (p<0.001). All three vitamins were higher in first trimester in cesarean delivery group. In contrast, ferritin levels were similar between two groups.

Table 3. Comparision of delivery way with respect to vitamin levels

	Caeserian section (n=134)	Vaginal delivery (n=365)	p
25OH-vitamin D (ng/dl)	12 (2-41.62)	8.33 (2-44)	**<0.001**
Vitamin B_{12} (pg/ml)	202 (78-890)	168 (44-583)	**<0.001**
Ferritin (ng/ml)	10.25 (2.7-234)	11.34 (1.53-344)	0.715
Folic Acid (ng/ml)	6.73 (1.4-28)	5.12 (1.11-22)	**<0.001**

The relationship between vitamin levels and meconium presence was represented in Table 4. 25OH-vitamin D and vitamin B_{12} levels were significantly low in the presence of meconium (p<0.001) whereas the level of ferritin was significantly high in the presence of meconium (p=.0.001). In addition, folic acid level was also significantly low in the presence of meconium (p=0.031)

Table 4. The relationship between vitamin levels and meconium presence

	Meconium (+) (n=63)	Mekonyum (-) (n=436)	*p*
25OH-vitamin D (ng/dl)	4 (2-44)	9.55 (3-41.62)	**<0.001**
Vitamin B_{12} (pg/ml)	123 (55-567)	189 (44-890)	**<0.001**
Ferritin (ng/ml)	20 (3-344)	10 (1.53-94.6)	**0.001**
Folic Acid (ng/ml)	5 (1.9-15.6)	5.87 (1.11-28)	**0.031**

In Table 5 we presented the relationship between vitamin levels and NICU need. 25 OH-vitamin D (p=0.001), vitamin B_{12} (p<0.001) and ferritin (p<0.001) levels were significantly low in mothers of newborns hospitalized in NICU. In contrast, folic acid level was similar between two groups (p=0.066).

We performed correlation analysis to show if there was a relationship between vitamin levels and pregnancy results in Table 6. There was a positive correlation between 25OH-vitamin D level and birthweight (p<0.001 r=0.615), 0. minute

apgar score (p<0.001 r=0.292) and 5. minute apgar scores (p<0.001 r=0.315). Also, there was a positive correlation between vitamin B_{12} and birthweight (p<0.001 r=0.314), 0. minute apgar score (p<0.001 r=0.243) and 5. minute apgar scores (p<0.001 r=0.232). Moreover, there was a positive correlation between folic acid levels and birthweight (p<0.001 r=0.339), 0. minute apgar score (p=0.033 r=0.095) and 5. minute apgar scores (p=0.025 r=0.100). In contrast to other vitamin levels there was a negative correlation between ferritin and 0. minute apgar score (p=0.004 r=0.128) and 5. minute apgar scores (p=0.005 r=0.125).

Table 5. The relationship between vitamin levels and NICU need

	NICU (+) (n=40)	NICU (-) (n=459)	p
25OH-vitamin D (ng/dl)	4.5 (2-44)	9 (2-41.62)	**0.001**
Vitamin B_{12} (pg/ml)	127.5 (55-567)	180 (44-890)	**<0.001**
Ferritin (ng/ml)	37.35 (3-344)	9.92 (1.53-94.6)	**<0.001**
Folic Acid (ng/ml)	4.47 (1.9-15.6)	5.8 (1.11-28)	0.066

NICU: neonatal intensive care unit

Table 6. The correlation between vitamins and variables

	25OH-vitamin D	Vitamin B_{12}	Ferritin	Folic acid
Age	**p=0.001 r=0.147**	**p=0.006 r=0.123**	p=0.998 r<0.001	p=0.092 r=0.075
Gravida	**p=0.011 r=0.113**	P=0.051 r=0.088	P=0.946 r=-0.003	p=0.128 r=0.068
Parity	**p=0.011 r=0.113**	P=0.051 r=0.088	P=0.946 r=-0.003	p=0.128 r=0.068
Birth weight	**p<0.00 r=0.615**	**p<0.001 r=0.314**	p=0.415 r=0.037	p<0.001 r=0.339
0. min. Apgar score	**p<0.001 r=0.292**	**p<0.001 r=0.243**	**p=0.004 r=-0.128**	**p=0.033 r=0.095**
0. min. Apgar score	**p<0.001 r=0.315**	**p<0.001 r=0.232**	**p=0.005 r=-0.125**	**p=0.025 r=0.100**

r= correlation coefficient, p=statistical significance

Data analysis was performed in the SPSS 25 (Statistical Package for Social Sciences) package program. Results for P <0.05 were considered statistically significant. Descriptive statistics were shown as median (minimum-maximum) for numerical variables and as number of observations and (%) for nominal variables.

The normality of the distribution of numerical variables was investigated by Kolmogorov Smirnov test. Whether there was a statistically significant difference between the two groups in terms of numerical variables was evaluated using the Mann-Whitney U test. The correlation between vitamin levels and variables was evaluated by determining Spearman's "rho" coefficient and significance level (p).

4. Discussion

Folic acid and vitamin B_{12} play an important role in generating S-adenosyl methionine, a major methyl donor for all methylation reactions. Deficiency of these vitamins leads to increased homocysteine levels, which may cause increased oxidative stress and adverse pregnancy outcomes (6, 7). The physiological functions of folic acid include DNA replication, cell proliferation and antioxidant protection. It is important also in angiogenesis, placental development, invasion of trophoblasts, and matrix metalloproteinase secretion (8). Vitamin B_{12} is transported by transcobalamin II, which is produced by the human placenta. Moreover, the human placenta has receptors for binding transcobalamin (9). Similarly, to the study of Finkelstein et al, in our study, the levels of folic acid and vitamin B_{12} were lower in meconium positive group and NICU (+) group showing increased fetal distress (10). In some studies, it was shown that altered maternal folate, vitamin B_{12} and resultant increased homocysteine levels exist in women giving preterm birth (11,12). But in our study only pregnant women≥37 weeks were included and because of this we did not evaluate the effects of low folic acid and vitamin B_{12} levels on preterm delivery. 25OH-vitamin D is essential for calcium and phosphate metabolism. It was shown that the placenta and decidua express the nuclear vitamin D receptor (VDR) and it is also important for fetoplacental development (13). However, the studies about the impact of hypovitaminosis D in the development of pregnancy complications has conflicting results (14,15). In a study it was shown that the Apgar scores were not affected from 25OH-Vitamin D levels (16). In contrast, at our study there was a positive correlation between high 25OH-Vitamin D levels and higher Apgar scores. With regards to caesarean section (CS), an association was found in our study between high 25OH-Vitamin D and increased risk of caesarean section rates which was contrast to Zhou et al results (17). Also, in a study done by Merewood et al. there was an increased risk of caesarean section rates in women with low 25OH-Vitamin D levels (18). Increase in the CS rate in patients with high vitamin D level may be due to cephalo-pelvic disproportion. The most common hematological problem encountered in pregnancy is anemia. Because of increased demand for oxygenation and fetal requirements, iron supplementation is needed (19). In our study, ferritin level was significantly high in the presence of meconium (p=.0.001). It may be due to increased incidence of isolated oligohydramnios which was shown by Korkmaz et al. (19). Iron overload is thought to favor oxidative stress which may trigger fetal stress increasing NICU need as in our study.

Adequate vitamin levels in the first trimester of pregnancy are crucial for a healthy pregnancy and newborn. A healthy balanced diet during pregnancy, is the best source of adequate supply. Inadequate or high levels of certain vitamins can cause unwanted pregnancy outcomes.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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