Research Article / Araştırma Makalesi

The Frequency of Vitamin B12 and Folic Acid Deficiency in Mothers and Their Newborn Infants in Şanlıurfa Province

Şanlıurfa'da Anne ve Yenidoğan Bebeklerinde B12 ve Folik Asit Eksikliğinin Sıklığı

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Abstract

Background: Vitamin B12 and folic acid deficiency in pregnant women is an important health issue which not only affects mothers but also their infants. The aim of this study is to reveal the frequency of vitamin B12 and folic acid deficiency in pregnant women and their newborn babies, to evaluate the relationship between maternal and neonatal vitamin B12 and folic acid levels, and to determine the risk factors for their deficiencies.
Materials and Methods: This prospective study included 600 pregnant women (gestational age: 38-42 weeks) who presented to obstetrics departments in Şanlıurfa Province and their newborn infants without perinatal complication (birth weight≥2500 g). The lower limit for vitamin B12 was defined as 200 pg/mL. Also, the lower limit for folic acid was defined as 5 ng/ml. Data regarding age, number of child, medication, comorbid disease or being vegetarian or not were recorded in all mothers.
Results: Vitamin B12 level was found below 200 pg/ml in 73.8% (443) of the pregnant women included in the study, and between 200-300 pg/ml in 22.7% (136). Vitamin B12 levels were found to be below 200 pg/ml in 70.5% (423) of newborns, and between 200-300 pg/ml in 23.2% (139). On the other hands, the folic acid level was below 5 ng/ml in 10.3% (62) of the pregnant women, it was observed that the folic acid level was below 5 ng/ml in 3.7% (22) of the newborns. There was a significant positive correlation between the vitamin B12 level of the mothers and the vitamin B12 level of the newborns (r=0.913, p<0.0001). Also, there was a significant positive correlation between the mothers' folic acid level and the newborns' folic acid level (r=0.026, p<0.0001).
Conclusions: As a result, it has been shown that a significant portion of newborns in Turkey have vitamin B12 deficiency. Vitamin B12 levels were quite low in mothers who gave birth recently. The deficiency of vitamin B12, which plays a major role in brain development upon intrauterine period, is a preventable cause of neurological deficit. Thus, it is highly important to screen and treat vitamin B12 deficiency before onset of clinical symptoms. We believe that our study is beneficial in this regard.

Key Words: Folic acid deficiency, Vitamin B12 deficiency, Newborns

Öz

Amaç: Gebelerde B12 ve folik asit vitamini eksikliği sadece anneleri değil bebeklerini de etkileyen önemli bir sağlık sorunudur. Bu çalışmanın amacı gebelerde ve yeni doğan bebeklerinde B12 vitamini ve folik asit eksikliği sıklığını ortaya koymak, maternal ve neonatal vitamin B12 ile folik asit düzeyleri arasındaki ilişkiyi değerlendirmek ve eksiklikleri için risk faktörlerini belirlemektir.
Materyal ve Metod: Bu prospektif çalışmaya Şanlıurfa ilinde kadın doğum polikliniğine başvuran 600 gebe (gebelik yaşı: 38-42 hafta) ve perinatal komplikasyonu olmayan (doğum ağırlığı ≥2500 g) yeni doğan bebekleri dahil edildi. B12 vitamini için alt sınır 200 pg/mL olarak tanımlandı. Ek olarak, folik asit için alt sınır 5 ng/ml olarak kabul edildi. Tüm annelerde yaş, çocuk sayısı, ilaç kullanımı, yandaş hastalık veya vejeteryan olup olmama ile ilgili veriler kaydedildi.
Bulgular: Çalışmaya alınan gebelerin %73,8 (443)'inde vitamin B12 düzeyi 200 pg/ml altında, %22,7 (136)'sinde 200-300 pg/ml arasında bulundu. Yenidoğan bebeklerin ise %70,5 (423)'inde vitamin B12 düzeyi 200 pg/ml altında, %23,2 (139)'sinde 200-300 pg/ml arasında saptandı. Öte yandan, gebelerin %10,3 (62)'ünde folik asit düzeyi 5 ng/ml altında bulunurken, yenidoğanların ise %3,7 (22)'sinde folik asit düzeyi 5 ng/ml altında olduğu görüldü. Annelerin vitamin B12 düzeyi ile yenidoğanların vitamin B12 düzeyi arasında anlamlı pozitif korelasyon vardı (r=0.913, p<0,0001). Ek olarak, annelerin folik asit düzeyi ile yenidoğanların folik asit düzeyi arasında anlamlı pozitif korelasyon vardı (r=0.026, p<0,0001).
Sonuç: Sonuç olarak Türkiye'deki yenidoğanların önemli bir kısmında B12 vitamini eksikliği olduğu gösterilmiştir. Yakın zamanda doğum yapan annelerde B12 vitamini seviyeleri oldukça düşüktü. Rahim içi dönemde beyin gelişiminde önemli rol oynayan B12 vitamini eksikliği, önlenebilir bir nörolojik defisit nedenidir. Bu nedenle, klinik semptomların ortaya çıkmasından önce B12 vitamini eksikliğinin taranması ve tedavi edilmesi oldukça önemlidir. Çalışmamızın bu açıdan faydalı olduğunu düşünüyoruz.

Anahtar Kelimeler: 12 vitamini eksikliği, Folik asit eksikliği, Yenidoğanlar

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Introduction

Vitamin B12 is a red-colored vitamin that dissolves in water, is synthesized mainly by microorganisms, and has various derivatives. Humans cannot synthesize the vitamin B12 they need, it is obtained from cobalamin in foods, especially animal foods. Since vitamin B12 is found in sufficient amounts in most animal foods, dietary deficiency is rare in normal diets. However, if there is not enough dietary intake, vitamin B12 deficiency is seen (1). Folic acid, on the other hand, is a heat-labile, water-soluble vitamin, especially abundant in green leafy plants (2).

The most important function of vitamin B12 together with folic acid is to provide DNA synthesis, which is necessary for cell division and proliferation (1). In addition to its role in the DNA synthesis, the vitamin B12 is a cofactor that plays role in methylation, neurotransmitter synthesis, homocysteine/methionine cycle. It is an essential vitamin that exists as cobalamin in foods, particularly in those of animal origin. The vitamin B12 deficiency may be present in breastfed infants of mothers with vitamin B12 deficiency (2).

The children below 2 years of age with low socioeconomic level are at risk. The vitamin B12 deficiency can lead more severe consequences in neonatal period and infancy where growth is accelerated than symptoms seen in other periods (3). While vitamin B12 deficiency in children may present with non-specific clinical findings such as fatigue, weakness, stomatitis, diarrhea or irritability, severe anemia with developmental delay, mental-motor retardation, ataxia, paresthesia, hyporeflexia, clonus, muscle wasting, and acquired motor and mental functions (sitting), walking, talking, laughing, etc.), convulsions and coma in advanced stages (4-6). Neurological findings can occur without hematological sign in more than 25% of patients with vitamin B12 deficiency (7). The most common cause of vitamin B12 deficiency during infancy in Turkey is vitamin B12 deficiency during pregnancy. Although vitamin B12 deficiency may be present at neonatal period, it can be overlooked as anthropometric measures aren't affected (8). The vitamin B12 is actively transported from mother to fetus during pregnancy. In healthy newborns, vitamin B12 depots of 25-50 µg can be sufficient over 6-12 months (9). The Institute of Medicine reported that the "Recommended Daily Allowance" (RDA) ranges from 0.4 mcg for age< 6 months to 2.4 mcg for adults and they suggested that the "Estimated Average Requirement" (EAR) and RDA during pregnancy women be 2.2 µg/day and 2.6 µg/day, respectively (10).

A healthy individual's body contains 500-200,000 micrograms (µg) of folic acid. Folic acid intake of 50-100 µg/day is required to meet the daily breakdown, loss with urine and bile. Otherwise, deficiency symptoms will appear within 4 months (8). Nutritional habits, drug use (such as antibiotics, anticonvulsants) and gastroenterological symptoms (such as malabsorption, diarrhea) should be questioned in the history of the patient with folic acid deficiency (8).

In our study, we aimed to reveal the frequency of vitamin B12 and folic acid deficiency in pregnant women and newborns and to evaluate the relationship between mothers and newborns. In addition, we aimed to evaluate the relationship between vitamin B12 and folic acid levels and socioeconomic level (SEL), birth, vitamin and iron supplementation in pregnant women and to evaluate newborn vitamin B12 and folic acid deficiency according to maternal vitamin B12 and folic acid deficiency.

Materials and Methods

In this prospective study, 600 pregnant women (gestational age: 38-42 weeks) and newborn babies without perinatal complications (birth weight ≥2500 g) who applied to the gynecology and obstetrics services of Harran University Faculty of Medicine, Şanlıurfa Maternity Hospital and existing private hospitals in Şanlıurfa province. was included. Exclusion criteria were multiple pregnancy, preterm birth, placenta previa, ablatio placentae, preeclampsia, bleeding (gastrointestinal, urinary) and low birth weight (<2500 g).

All subjects gave written informed consent. For all pregnant women, a questionnaire was completed to collect data regarding age, weight, gravidity, parity, gestational age, educational level, occupation, vitamin and iron supplementation use during pregnancy and SEL. Again, Socioeconomic Level Scale (SLS) modified by Toukan et al. (11) was used to assess socioeconomic level. The birth weight, height and gender were recorded in all newborns.

In the SLS, the following items were assessed: living in a concrete building, 5 points; using tap water, 3 points; appropriate protein intake by diet, 2 points; having a refrigerator, 5 points; having a washing machine, 5 points; having a dish washer, 7 points; having a radio , 1 point; having a TV, 1 point; having phone, 5 points; having a car, 2 points; toilet in the house, 1 point; central heating, 1 point; living in own house, 1 point. The SEL was defined as follows according to total SLS score: 0-20 points, low; 21-25 points; low-to-moderate; 26-30 points, moderate-to-high; and 31-40 points, high (11).

Blood samples were taken from all pregnants 1-3 hours before delivery. In newborns, blood samples were taken from the umbilical cord at birth. All samples were drawn into vacuum tubes without EDTA (potassium-2 ethylenediaminetetraacetic acid) and centrifuged at 4000 rpm over 10 minutes. Sera obtained were stored at -80°C until assays. In the samples, folic acid and vitamin B12 levels were studied by automated analyzer (E-170 Roche®, Germany) using ECLIA (electrochemiluminescence) method at the Laboratory of Biochemistry Department of Harran University, Medicine School.

The vitamin B12 level<200 pg/mL (<148 pmol/L) was defined as deficiency in both groups while vitamin B12 levels of 200-300 pg/mL (148-221 pmol/L) were considered was low-normal and those ≥300 pg/mL (>221 pmol/L) as normal.

The folic acid levels<5 ng/mL were defined as deficiency while those >5 ng/ml were considered as normal (12-14).

The study was approved by Institutional Ethics Committee of Harran University, Medicine School (approval#: 20.03.2015, 15/03/18). The study was conducted in accordance to tenets of Helsinki Declaration.

Statistical analysis

Data were analyzed using SPSS for Windows 20.0. The comparisons were performed using Mann Whitney U test, Kruskal-Wallis test, Fisher's exact test, Independent sample's t test, Paired sample's t test, one-way ANOVA and Chi-square tests. Correlation analyses were performed using Pearson's correlation test. A p value<0.05 was considered as statistically significant.

Results

Mean age of pregnant women was 30.02±6.24 years (min-max: 15-44 years; median age: 30 years). In newborns, mean height was 50.15±1.35 while mean weight was 3235.62±314.61 g. Of the newborns included, 55.7% (n=334) were girls and 44.3% (n=266) were boys. No congenital anomaly was detected in newborns.

Average vitamin B12 and folic acid levels in pregnant women 160.50±103.27 pg/mL and 11.37±6.23 ng/mL while mean hemoglobin and mean corpuscular volume (MCV) were 10.95±1.54 g/dL and 82.30±6.81 fL, respectively (Table 1).

Table 1. Maternal Hematological Values, Vitamin B12 and Folic Acid Values

Hematology	Mean±SD
Hemoglobin	10.95 ± 1.54
Hematocrit	34.67±3.98
MCV	82.30±6.81
RDW	14.24±3.02
RBC	4146.30±677.80
Vitamin B12	160.50±103.27
Folic Acid	11.37±6.23

SD: Standard deviation; RBC: Red blood cell; MCV: mean corpuscular volume; RDW: Red cell distribution width

In the pregnant women included, vitamin B12 level was <200 pg/mL in 73.8% (n=443) while it was 200-300 pg/mL in 22.7% (n=136) and >300 pg/mL in 3.5% (n=21). In the newborns, vitamin B12 level was <200 pg/mL in 70.5% (n=423) while it was 200-300 pg/mL in 23.2% (n=139) and >300 pg/mL in 6.3% (n=38). On the other hands, in the pregnant women included, folic acid was <5 ng/mL in 10.3% (n=62) while >5 ng/mL in 89.7% (n=538). In the newborns included, folic acid was <5 ng/mL in 3.7% (n=22) while >5 ng/mL in 96.3% (n=578) (Table 2).

There was a significant, positive correlation between maternal and neonatal vitamin B12 levels (r=0.913; p<0.0001). Again, there was a significant positive correlation between maternal and newborn folic acid levels (r=0.026; p<0.0001).

The parity was one in 74 (12.3%), 2 in 101 (16.8%), 3 in 111 (18.5%), 4 in 115 (19.2%) and ≥5 in 198 (32.9%) of the pregnant women. The vitamin B12 level was 164.63±109.86 in women with parity of 0-5 while 142.51±64.78 in those with parity ≥6, indicating a significant difference (p<0.005).

Table 2. Vitamin B12 and Folic Asid Levels of Pregnant and Newborns

	Deficiency n (%)	Low-normal n (%)	Normal n (%)
Pregnant (vitamin B12)	443 (73.8%)	136 (22.7%)	21 (3.5%)
Newborn (vitamin B12)	423 (70.5%)	139 (23.2%)	38 (6.3%)
Pregnant (folic asid)	62 (%10.3)	-	538 (%89.7)
Newborn (folic asid)	22 (%3.7)	-	578 (%96.3)

When supplemental vitamin and iron preparation use were assessed, it was seen that 198 pregnant women (32.8%) used one or two of these preparations regularly while 245 (40.8%) used in an irregular manner and 157 (26.4%) used no vitamin or iron preparation. When vitamin B12 levels were assessed according to duration of vitamin and iron supplementation, it was found that the vitamin B12 level was significantly higher in pregnant women regularly taking vitamin and iron supplementation compared to those not taking any supplementation (184.76±109.43 vs. 152.26±133.67; p=0.008). It was also seen that vitamin B12 level was significantly higher in pregnant women regularly taking vitamin and iron supplementation than those taking irregular manner (184.76±109.43 vs. 146.18±66.03; p=0.000). No significant difference was observed in folic acid levels according to duration of vitamin or iron supplementation (p=0.148 for regular vs. no drug use; p=0.538 for regular vs. irregular drug use; p=0.601 for irregular vs. no drug use).

When pregnant women were stratified according to SEL, it was found that the SEL was low in 164 (27.4%), low-moderate in 256 (42.7%), moderate-to-high in 122 (20.3%) and high in 58 (9.7%). When vitamin B12 level was compared according to SEL, it was seen that vitamin B12 level was significantly lower in low SLS score than those with high SLS score (144.01±59.77 vs.. 196.48±84.49; p<0.004) (Table 3). No significant difference was found in folic acid levels according to SEL (Table 4).

Table 3. Distribution of mothers Vitamin B12 values by socioeconomic level

SLS	Deficiency n (%)	Low-normal n (%)	Normal n (%)
Low	139 (84.8%)	21 (12.8%)	4 (2.4%)
Low-moderate	212 (82.8%)	40 (15.6%)	4 (1.6%)
Moderate-to-high	66 (54.1%)	47 (38.5%)	9 (7.4%)
High	26 (44.8%)	28 (48.3%)	4 (6.9%)

SLS:Socioeconomic Level Scale

Table 4. Distribution of mothers' folic acid levels by socioeconomic level

SLS	Deficiency n (%)	Normal n (%)
Low	18 (11%)	146 (89%)
Low-moderate	24 (9.4%)	232 (90.6%)
Moderate-to-high	10 (8.2%)	112 (91.8%)
High	10 (17.2%)	48 (82.8%)

Discussion

Vitamin B12 deficiency was first reported by Jadhav et al. (15) it was described by in 1962. Although primary deficiency is rare in children, it usually develops due to maternal deficiency or juvenile pernicious anemia. Vitamin B12 deficiency present during pregnancy and lactation reduces the vitamin B12 content of breast milk and leads to vitamin deficiency in fetus and newborn. Although vitamin B12 deficiency is seen in all age groups, it is more common in societies with low socioeconomic status (16, 17).

Previous studies have reported that the main cause of vitamin B12 deficiency in infants is maternal vitamin B12 deficiency. In a study at Southeast region of Turkey, Koç et al. (18) found that vitamin B12 frequency was 72.3% in pregnant women and 41.2% in newborns; however, authors observed no folic acid deficiency in newborns. In a study conducted on 250 pregnant women and their newborn babies, vitamin B12 deficiency was found in 81.6% of mothers and 42% of newborns (3). Ertaş et al. (19) in a study screening vitamin B12 deficiency in primary healthcare facilities in Şanlıurfa province, found vitamin B12 deficiency frequency as 40% in 211 healthy infants

aged 6-11 months. Authors observed maternal vitamin B12 deficiency in 75% of infants with deficiency and in 51% of infants with normal vitamin B12 level ($p<0.05$) (19). In previous studies, markedly low maternal and neonatal vitamin B12 levels were reported in agreement with our study.

In our study, a positive correlation was detected between vitamin B12 levels of pregnant women and newborns. Similarly, a correlation was detected between maternal and neonatal vitamin B12 levels in studies by Koç et al. (18), Guerra-Shinohara et al. (20), Monsen et al. (21), Guiglani et al. (22) and Sayar et al. (23) ($r=0.395$, $r=0.68$, $r=0.51$, $r= 0.730$ and $r=0.675$; $p<0.01$ for all). In our study, a relationship was found between folic acid levels of mothers and newborn babies. In the study of Koç et al. (18), Guerra-Shinohara et al. (20), Guiglani et al. (22) and Sayar et al. (23) a positive correlation was found between pregnant and newborn folic acid levels, similar to our study ($r=0.227$, $r=0.55$, $r=0.361$ and $r=0.499$, respectively; $p=0.017$and $p<0.01$, respectively).

In our study, we found that mean vitamin B12 level was significantly higher in newborns (174.62±114.36) than pregnant women (160.50±103.27). Similarly, in 1993 in Greece Schulpis et al. (24) in their study on pregnant women, the average vitamin B12 level in newborns was found to be higher than in pregnant women, from Norway on 173 pregnant women and newborns Monsen et al. (21), from Brazil on 69 pregnant women and newborn Guerra-Shinohara et al. (20), from Şanlıurfa, Turkey on 180 pregnant women and newborn Koç et al. (18), from Edirne, Turkey on 250 pregnant women and newborns Sayar et al. (23) and Giugliani et al (22) from Brazil on 51 pregnant women and newborns.

In pregnant women, the mean hemoglobin level was reported as 11.7±1.47 g/dL and 11.6±1.47 g/dL in studies from İstanbul Büyükyazı et al. (25), in a study from Edirne Sayar et al. (23), 11.89±1.16 g/dL in a study from İzmir Akça et al. (26), 12.3±1.49 g/dL in a study from Erzurum Eryılmaz et al. (27), 11.2±0.15 in a study from Ankara Erdoğan et al. (28) and 13.8±1.5 g/dL in a study from Norway Bratlid and Moe (29). In our study, it was found that mean hemoglobin level was 10.95±1.54 g/dL in agreement with those reported in the studies from different regions of Turkey.

In a study from Greece, Schulpis et al. (24) found that vitamin B12 levels were significantly low in both mothers and their newborns in an immigrant population with low socioeconomic level. In a study from Ankara province, no significant correlation was detected between vitamin B12 level and socioeconomic level in pregnant women at second and third trimester (28). In our study, the finding of significant correlation between B12 and socioeconomic level was attributed to better prenatal follow-up, regular use of vitamin supplementation and higher awareness about nutrition.

Although there was no vegetarian patient in our study, high rate of patients with low vitamin B12 level in mothers and their infants might be caused by sufficient vitamin B12 intake due to low socioeconomic level. In a study conducted on 250 pregnant women and their newborns in Edirne, unlike our study, no significant relationship was found between parity and vitamin B12 levels (23). However, there are studies supporting a correlation between parity and maternal vitamin B12 levels in the literature. This may be due to regional cultural variation , insufficiency in family planning and high parity (mean parity: 3.75±1.9) in our study.

Vitamin B12 levels were found to be significantly higher in mothers and their babies who took regular vitamin or iron supplements ($p=0.008$ and $p=0.002$). Based on this finding, multivitamin preparations used regularly during pregnancy have a positive effect on newborn vitamin B12 levels because they increase the mother's vitamin B12 stores. In the literature, oral and intramuscular vitamin B12 therapy was compared in patients with megaloblastic anemia. In a study by Bolaman et al. (30) 60 adults patients received oral and intramuscular therapy were followed over 90 days and it was reported that treatment responses were comparable in both groups. In an adult study, Kuzminski et al. (31) reported similar efficacy for both preparations. These studies showed that oral vitamin B12 intake was not inferior than intramuscular treatment and supported the finding that vitamin B12 level was significantly higher in patients received vitamin preparations in regular manner.

In our study, the frequency of folic acid deficiency in the Şanlıurfa region was found to be 10.3% in pregnant women, while the frequency of folic acid deficiency in newborns was 3.7%. In a study conducted in the Edirne region of 250 pregnant women and their newborn babies, the frequency of folic acid deficiency was found to be 22.4% in pregnant women, while folic acid deficiency was not observed in newborns (23). In a study conducted by Açkurt et al. (32) in the Izmit region, the frequency of folic acid deficiency was found to be 59.7% in early pregnancy and 76.4% in late pregnancy. This supports the view that the levels of folic acid, which has been shown in previous studies, decrease even if the intake is sufficient during pregnancy (33, 34). In our study, a statistically significant relationship was found between maternal folic acid levels and infant folic acid levels ($r=0.026$, $p<0.0001$). Koc et al. (18), Sayar (23), Guerro-Shinohara et al. (20), Giugliani et al. (22) found a positive correlation between serum folic acid levels in pregnant women and newborns, similar to our study.

A limitation of this study was that maternal folate and vitamin B12 status were only looked at prenatally once, not longitudinally throughout pregnancy. In addition, the diagnosis of vitamin B12 deficiency had to be reinforced with serum or urine MMA level.

Conclusion

Our study showed that vitamin B12 deficiency is high in mothers and newborn babies in Şanlıurfa province and newborn vitamin B12 levels are closely related to maternal levels. Our study is valuable in that it correlates newborn vitamin B12 and folic acid levels with maternal levels and demonstrates by sampling a large number of newborns. Vitamin B12 and folic acid deficiency, which have an important place in brain development from the intrauterine period, is a preventable cause of neurological deficit. For this reason, the importance of screening and treatment before clinical symptoms occur is very important. We think that our study is useful in this regard.

Ethical Approval: *The study was approved by Institutional Ethics Committee of Harran University, Medicine School (approval#: 08.05.2015/15066). The study was conducted in accordance to tenets of Helsinki Declaration.*

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Concept: N.A., A.C.
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Data acquisition: N.A.
Analysis and interpretation: N.A., A.C.
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