# How Does Folic Acid Supplementation Affect Serum Folate Concentrations in Pregnant Turkish Women?

# Folik Asit Takviyesi Türk Toplumunda Gebelerde Serum Folat Düzeyini Nasıl Etkilemektedir?

Folate Levels in Pregnancy

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**Özet**

Amaç: Folik asit takviyesinin Türk toplumunda gebelerin serum folat düzeyleri üzerine etkisinin belirlenmesi amaçlanmıştır. Gereç ve Yöntem: Toplam 397 hastanın klinik kayıtları retrospektif olarak incelendi. Folik asit takviyesi yapılıp yapılmamasına göre hastalar 2 gruba ayrıldı: Grup 1 (n=294), gebelikten önce veya gebelik sırasında folik asit takviyesi kullanmamış hastalar, Grup 2 (n=103) gebelik öncesinden başlayarak düzenli olarak hergün 400 mcg kullanan hastalar. Gruplar demografik ve laboratuar veriler açısından karşılaştırıldı. Bulgular: Gebelik öncesi ve gebelik sırasındaki hemoglobin, serum kalsiyum ve serum folat seviyeleri her 2 grupta benzer olarak saptandı (sırasıyla p=0.544, p=0.549, p=0.289, p=0.299, p=0.072 ve p=0.061). Grup 1 için gebelik öncesi ve gebelik sırasındaki folat konsantrasyonları arasında istatiksel olarak anlamlı fark saptanmadı (p=0.059). Grup 2 için gebelik öncesinde ve gebelik sırasında folat konsantrasyonları istatistiksel olarak benzerdi (p=0.057). Molar gebelik, intrauterin ölüm, nöral tüp defekti, ventriküler septal defect, fetal büyüme kısıtlılığı, preeklampsi, preterm doğum, doğum ağırlığı, yenidoğan yoğun bakım gereksinimi, 1. ve 5. dakika Apgar skorları gibi perinatal sonuçlar bakımından gruplar benzer olarak saptandı (sırasıyla p=0.760, p=0.576, p=0.382, p=0.553, p=0.452, p=0.940, p=0.683, p=0.855, p=0.710, p=0.910 ve p=0.924). Tartışma: Mevcut çalışmanın bulguları, gebe kadınlarda sadece günlük beslenme alışkanlıklarıyla serum folat düzeylerinin 4.5 ng/ml üzerinde tutulabildiğini düşündürmektedir.

**Anahtar Kelimeler**

Folik Asit; Gebelik; Prenatal Takviye

**Abstract**

Aim: To determine the effect of the use of folic acid supplementation on serum folate levels in Turkish pregnant women. Material and Method: Clinical records of a total of 397 patients were retrospectively examined. The patients were recruited into 2 groups based on folic acid supplementation. Group 1 included 294 women who did not take any folic acid tablets before or during pregnancy and Group 2 consisted of 103 women who regularly took 400 mcg of folic acid daily, starting from the preconception period. Both groups were compared with respect to demographic and biochemical characteristics. Results: The patients in Group 1 and 2 had statistically similar pre-pregnancy and pregnancy hemoglobin, pre-pregnancy and pregnancy serum calcium, and pre-pregnancy and pregnancy serum folate concentrations (p=0.544, p=0.549, p=0.289, p=0.299, p=0.072, and p=0.061 respectively). No statistically significant difference was determined between pre-pregnancy and pregnancy folate concentrations in Group 1 (p=0.059). Pre-pregnancy and pregnancy folate concentrations were statistically similar in Group 2 (p=0.057). Both study groups were determined as statistically similar with respect to perinatal outcomes, including molar pregnancy, intrauterine demise, neural tube defects, ventricular septal defect, fetal growth restriction, preeclampsia, preterm birth, birth weight, neonatal intensive care unit admission, and 1st minute and 5th minute Apgar scores (p=0.760, p=0.576, p=0.382, p=0.553, p=0.452, p=0.940, p=0.683, p=0.855, p=0.710, p=0.910, and p=0.924 respectively). Discussion: Based on the findings of the present study, it may be considered that serum folate concentrations in pregnant women can be maintained by dietary intake alone of over 4.5 ng/ml.

**Keywords**

Folic Acid; Pregnancy; Prenatal Supplementation

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## Introduction

Folic acid is a water-soluble B complex vitamin that is made up of a pteridine ring system, p-aminobenzoic acid, and one molecule of glutamic acid (chemical name: pteroylglutamic acid). The folates in nature are pteroyl polyglutamic acids with 2 to 8 glutamic acid groups. If folic acid is included in vitamin supplements and fortified foods, it is frequently in the synthetic and stabilized form which is named folate. The active form of folate in the human body, tetrahydrofolic acid, participates as a coenzyme in several essential metabolic reactions. This coenzyme also acts as a vital component in the generation of blood cells and the synthesis and repair of genetic materials that contain nucleic acids [1-5].

Leafy green vegetables, spinach, fruits, and organ foods such as liver are sources rich in folate. Polyglutamates are the most common forms of folate in foods. Absorption of polyglutamates takes place in the proximal small intestines upon conversion into monoglutamates. The body is able to absorb only about 50% of dietary folate. This problem is further complicated by cooking, processing, and storage practices [4-7].

Food fortification of grain products has been introduced in many countries to increase folic acid intake. It has been estimated that the folic acid absorption rate is 85% from fortified foods including flour, rice, pasta, bread, and breakfast cereals [8]. However, there is no practice of food fortification with folic acid in Turkey. Instead, commercially available vitamin tablets with folic acid are prescribed for pregnant women. Folic acid is available in different doses in multivitamin tablets or in tablets only containing folic acid [9]. It has been reported that folic acid absorption rate is 100% from multivitamin supplements [10].

The present study aimed to determine the serum folate concentrations of Turkish women in the first trimester of pregnancy in respect to the utilization of vitamin supplements.

## Material and Method

This retrospective study was conducted at Pazarcık State Hospital, which is a secondary level hospital. Approval for the study was granted by the Ethics Committee of Kahramanmaras Sutcu Imam University Hospital.

A retrospective examination of medical records between January 2010 and December 2014 was conducted to determine patients whose pre-pregnancy and first trimester serum levels of folate, iron and calcium, and hemoglobin levels were available from their medical records. Patients for whom we only had second or third trimester measurements were not included in the study since the physiological increase in plasma volume becomes prominent especially in the 2nd and 3rd trimesters of pregnancy, which may lead to a decrease in serum levels of the measured parameters. By these inclusion criteria, 397 patients were identified and grouped retrospectively according to the receipt of periconceptional folate supplementation at a dosage of 400 mcg. Group 1 included 294 women who did not take any folic acid tablets before or during pregnancy and Group 2 consisted of 103 women who regularly took 400 mcg of folic acid daily, starting from the preconception period.

Women with congenital heart diseases, epilepsy, a body mass index (BMI) of <19 kg/m2 or >29.9 kg/m2, those who had been diagnosed with acute or chronic diseases (hypertension, diabetes mellitus, renal insufficiency, hepatic diseases, infections, and immunological disorders), those who were on a vegetarian diet, who smoked, or who had a history of a fetus with neural tube defect were excluded from the study. Women who abused alcohol, who were taking anti-cancer, immunosuppressive or anticoagulant drugs, and those who were taking other medications containing zinc or iron were also excluded.

Serum folate concentrations were measured using chemiluminescent microparticle immunoassay technology on an Architect 12000 analyzer (Abbott Diagnostics, IL, USA).

Folate deficiency is diagnosed if the serum folate level is <4.5 ng/ml. The World Health Organization (WHO) recommends that erythrocyte folate concentrations should be > 400 ng/ml in women of reproductive age so that neural tube defects can be reduced to a minimum. Therefore, WHO recommends using erythrocyte folate threshold of >400 ng/ml as an indicator for folate deficiency. However, no serum folate threshold is recommended to prevent neural tube defects for women of reproductive age in the general population. To what extent serum folate levels reflect folate deficiency is a matter of debate [11].

Data related to age, BMI, gravidity, parity, consanguinity, and perinatal outcomes of the participants were acquired from their hospital records. Pre-pregnancy and pregnancy serum hemoglobin, iron, calcium, and folate concentrations of the participants were also retrieved from the medical files.

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS IBM Software, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables were denoted as numbers or percentages where appropriate. The Kolmogorov-Smirnov test was used to test the distribution of variables. The Student t test, paired samples t test, Mann Whitney U test, and Wilcoxon test were utilized for comparisons. Two-tailed p values less than 0.05 were accepted as statistically significant.

## Results

The demographic characteristics of the two groups are presented in Table 1. The women in Groups 1 and 2 were statistically similar with respect to age, body mass index, consanguinity, gravidity, parity, and gestational age (p=0.338, p=0.895, p=0.143, p=0.896, p=0.833, and p=0.103 respectively).

Table 1. Demographic Data of the Patients

| | Group 1 (n=294) | Group 2 (n=103) | P value |
|---|---|---|---|
| Age (years) | 26.1 ± 5.9 | 26.7 ± 5.5 | 0.338 |
| Body mass index (kg/m2) | 24.8 ± 4.9 | 24.7 ± 3.9 | 0.895 |
| Consanguinity (n) | 61 (20.3%) | 14 (14.7%) | 0.143 |
| Gravidity | 2.5 ±1.3 | 2.5 ± 1.2 | 0.896 |
| Parity | 1.2 ± 1.1 | 1.3 ±1.1 | 0.833 |
| Gestational age (weeks) | 8.2 ± 2.2 | 7.8 ± 1.9 | 0.103 |

n: Number of patients (%)

The laboratory data of the study groups are presented in Table 2. The women who did not take any folic acid tablets before or during pregnancy and the women who regularly took 400 mcg of folic acid had statistically similar pre-pregnancy and pregnancy hemoglobin, pre-pregnancy and pregnancy serum calcium, and pre-pregnancy and pregnancy serum folate con-

Table 2. Laboratory Data of the Study Groups

| | Group 1 (n=294) | Group 2 (n=103) | P value |
|---|---|---|---|
| Pre-pregnancy hemoglobin (g/dl) | 11.9 ± 2.9 | 12.4 ± 2.1 | 0.544 |
| Pregnancy hemoglobin (g/dl) | 11.8 ± 3.1 | 12.1 ± 2.2 | 0.549 |
| Pre-pregnancy serum iron (µg/dl) | 75.2 ± 4.6 | 87.5 ± 9.1 | 0.040 |
| Pregnancy serum iron (µg/dl) | 74.8 ± 34.8 | 84.5 ± 57.9 | 0.045 |
| Pre-pregnancy serum calcium (mg/dl) | 10.0 ± 0.4 | 10.1 ± 0.4 | 0.289 |
| Pregnancy serum calcium (mg/dl) | 9.3 ± 0.3 | 10.2 ± 0.4 | 0.299 |
| Pre-pregnancy serum folate (ng/ml) | 10.0 ± 6.5 | 9.8 ± 4.7 | 0.072 |
| Pre-pregnancy folate deficiency | 21 (7.4%) | 8 (7.8%) | 0.828 |
| Pregnancy serum folate (ng/ml) | 9.2 ± 4.4 | 10.9 ± 3.7 | 0.061 |
| Pregnancy folate deficiency | 22 (7.5%) | 6 (5.8%) | 0.831 |

centrations (p=0.544, p=0.549, p=0.289, p=0.299, p=0.072 and p=0.061 respectively). Pre-pregnancy and pregnancy serum iron concentrations were determined to be statistically significantly lower in Group 1 than in Group 2 (p=0.040 and p=0.045 respectively). No statistically significant difference was determined between the pre-pregnancy and pregnancy folate levels in Group 1 (p=0.059). Pre-pregnancy and pregnancy folate concentrations were statistically similar in Group 2 (p=0.057).

Table 3 shows the comparison of the perinatal outcomes of the two study groups. The women in Groups 1 and 2 were statistically similar in respect to perinatal outcomes including molar pregnancy, intrauterine demise, neural tube defects, ventricular septal defect, fetal growth restriction, preeclampsia, preterm birth, birth weight, neonatal intensive care unit admission, and 1st and 5th minute Apgar scores (respectively p=0.760, p=0.576, p=0.382, p=0.553, p=0.452, p=0.940, p=0.683, p=0.855, p=0.710, p=0.910 and p=0.924).

Table 3. Perinatal Outcomes of the Study Groups

| | Group 1 (n=294) | Group 2 (n=103) | P value |
|---|---|---|---|
| Molar pregnancy | 4 (1.3%) | 1 (1.0%) | 0.760 |
| Intrauterine demise | 14 (4.8%) | 5 (4.9%) | 0.576 |
| Neural tube defects | 4 (1.3%) | 3 (3.0%) | 0.382 |
| Ventricular septal defect | 1 (0.3%) | 0 (0.0%) | 0.553 |
| Fetal growth restriction | 1 (0.3%) | 1 (1.0%) | 0.452 |
| Preeclampsia | 9 (3.1%) | 3 (2.9%) | 0.940 |
| Preterm birth | 22 (7.5%) | 9 (8.7%) | 0.683 |
| Birth weight | 3154.7±223.5 | 3227.8±318.9 | 0.855 |
| 1st minute Apgar score | 7.2±3.4 | 7.4±2.5 | 0.910 |
| 5th minute Apgar score | 9.0±2.5 | 8.8±2.6 | 0.924 |
| Neonatal intensive care unit admission | 25 (8.5%) | 10 (9.7%) | 0.710 |

## Discussion

It is well known that vitamin replacement offers a definitive cure in cases of vitamin deficiencies that may result in significant morbidity. Therefore, vitamin supplements have been traditionally considered to restore and nourish the health of consumers. The need for vitamins may increase during pregnancy and thus, vitamin deficiencies may have a negative impact on both the mother and fetus. However, the effects of vitamin supplements on non-deficient pregnant individuals are unclear [12].

In the most frequently adopted guidelines, it is advised that all women in the reproductive period should consume a healthy, folate-rich diet. Moreover, consultation should be provided to these women about the benefits of folic acid supplementation during medical well-being visits whether or not a pregnancy is planned. The reason for such counseling is that many pregnancies are unplanned and all women in the reproductive age group may become pregnant. This recommendation is based on clinical experience, descriptive studies, or reports of expert committees rather than on properly randomized controlled trials. That is, the opinions of respected authorities have been considered satisfactory enough to recommend folic acid supplementation in women of childbearing age [13, 14].

The aforementioned guidelines also emphasize that folic acid/multivitamin supplementation is needed to achieve the serum concentrations that are required to provide protection against neural tube defects. Therefore, women with a low risk for neural tube defects or congenital cardiac anomalies and women with low-risk male partners (male partners with no personal or family risk for NTD or folic acid-sensitive birth defects) should be advised to take an oral multivitamin supplement containing 0.4 mg folic acid daily for at least 2 to 3 months before conception, throughout the pregnancy, and for 4 to 6 weeks in the postpartum period. This recommendation is based on better-quality evidence obtained from well-designed cohort or case-control studies. Such evidence has been accepted as sufficient for the recommendation of folic acid supplements in women who wish to conceive [15, 16].

Normal mineral and vitamin metabolism is essential for successful pregnancies. However, there is a scarcity of well-designed, large-scale, and controlled studies of the utilization of folic acid supplements in pregnancy; practical implications of this issue are based on general recommendations rather than evidence-based information [17, 18].

Dietary studies can offer valuable data about the effects of vitamin intake on both the mother and fetus, but significant problems may arise in the interpretation and specification of their results. The first challenge is that dietary studies are generally designed as non-interventional population studies that allow the inclusion of large numbers of individuals. Yet, these studies usually review non-homogeneous and poorly defined populations which are not stratified in terms of demographic, social, and clinical characteristics. Moreover, accurate assessment of food intake and correct determination of individual food components is difficult and unreliable in non-interventional dietary studies [10, 19, 20].

The second challenge is that isolated deficiencies of dietary components are rarely encountered. Accordingly, individuals are recruited from the geographical areas with generally known dietary shortcomings and interventional dietary studies are conducted. These participants often have nutritional habits that result in the deficiency of several food components. Such a situation may have three consequences: the replacement of a single food component may be inadequate to get a clinical response; simultaneous replacement of several food components may result in harmful overdoses; and the probable occurrence of nutrient interactions may impair the efficiency of this replacement. Therefore, controlled studies should be carried out to evaluate the validity and reliability of the results obtained

from dietary studies [21].

The results of the present study indicated statistically similar pre-pregnancy and pregnancy serum folate concentrations for women who have never consumed folic acid supplements and women who have regularly taken folic acid tablets (p=0.072 and p=0.061 respectively). Both groups of women were similar in respect to perinatal outcomes including intrauterine demise, neural tube defects, ventricular septal defect, fetal growth restriction, preeclampsia, preterm birth, birth weight, neonatal intensive care unit admission, and Apgar scores (p=0.576, p=0.382, p=0.553, p=0.452, p=0.940, p=0.683, p=0.855, p=0.710, p=0.910 and p=0.924 respectively).

These findings imply that the women living within the study area have been able to maintain serum folate concentrations over 4.5 ng/ml by dietary intake alone. This interesting result can be attributed to the exclusion of any risk factor that may lead to folate deficiency. Another underlying factor may be the relatively low frequency of the 5, 10-methylenetetrahydrofolate reductase enzyme variant in the study cohort. This enzyme has a fundamental role in the transfer of a methyl group to homocysteine in order to make up methionine. The variant of 5, 10-methylenetetrahydrofolate reductase enzyme exists in about 5% to 15% of the general population and it can compromise tissue folate levels [22].

A clinical study conducted within the Tokat province of Turkey reported serum folate levels of 7.9 ng/ml for 246 adults (145 men and 101 women) with alopecia areata and serum folate concentrations of 7.4 ng/ml for 89 healthy adults [23]. These values are consistent with the serum folate concentrations of the pregnant women reviewed in this study.

The power of the current study is limited by several factors. The first factor is the relatively small cohort size. Neural tube defects occur in approximately 0.1% of all births and the cohort size of this study was insufficient to draw a conclusion about the effects of folate supplementation on congenital anomalies. Other factors include the retrospective nature of the pre-pregnancy biochemical values, the lack of data related to dietary habits, and the concentrations of other anemia markers including vitamin B12, ferritin, and transferrin.

Another limiting factor is that no threshold for serum folate concentration has been recommended for the prevention of neural tube defects in women of reproductive age. In fact, it has been advised to use the threshold value for erythrocyte folate concentration to establish the corresponding threshold value in serum [11]. To the best of our knowledge, there are no randomized controlled studies in the literature that focus on the dose of folic acid supplementation and the ideal serum folate concentration in women of childbearing age.

In conclusion, based on the results of the present study, it can be considered that pregnant women are able to maintain serum folate concentrations over 4.5 ng/ml by dietary intake alone without folic acid supplementation. This may provide a rationale for maintaining folic acid supplementation at a lower dose and not necessarily insisting on folic acid supplementation in populations with a low prevalence of folate deficiency.

Pre-pregnancy and early pregnancy folate supplementation has been firmly established as a part of prenatal care. However, the findings of studies conducted in geographical areas with a high prevalence of folate deficiency are particularly important as they may show that supplementation prophylaxis is effective. Further prospective large-scale research is warranted to understand the benefits of folic acid supplementation before pregnancy and during early gestation in Turkish women.

### *Competing interests*

The authors declare that they have no competing interests.

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