

# Molecule associated with autism: Folic acid. Do we use it correctly?

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## Abstract

**Aim:** Neural tube defects (NTD) are among most commonly found congenital anomalies. Sufficient amount of folic acid taken in preconception period is reported to prevent NTD development. There are studies in literature which make an association between high doses of folic acid taken during pregnancy and autism. When folic acid supplement began to be made on foods to protect from neural tube defects a concurrent increase has been mentioned in autism prevalence. Today pregnancy and folic acid supplement are currently indispensable. Physicians have made this supplement a routine.

Aim of study is to assess if every woman in Malatya has a deficiency which requires routine use of folic acid through the folic acid levels of women who refer to health institutions.

**Material and Methods:** Study conducted on the records of 1003 female patients in reproductive age group who referred to neurology and internal medicine polyclinics for any reason and whose folic acid levels were checked by the related physician.

**Results:** Serum folic acid level averages of all women whose records were taken is  $7,69 \pm 3,03$  ng/ml. Only 27 (2,69%) women's folic acid levels lower than 3,08 ng/ml. 699 (69,69%) women's serum folic acid levels higher than 6 ng/ml.

**Conclusions:** If these 1003 women were pregnant, they would routinely be started folic acid. However, folic acid levels of a great majority (69,69%) was found to be higher than 6 ng/ml. We believe that physicians should start folic acid after taking into consideration the nutritional habits and socioeconomic characteristics of the region they live in and after they check serum folic acid level.

**Keywords:** Folic Acid; Unnecessary Drug Usage; Malatya.

## INTRODUCTION

Neural tube, in which brain and medulla spinalis develop during the embryological period, should be closed at the end of intrauterine fourth week. When this closure does not take place, serious congenital anomalies such as anencephaly, meningocele, myelocoele and meningomyelocoele, which are called neural tube defects (NTDs), occur (1). NTDs are among most commonly found congenital anomalies (2). The frequency of neural tube defects is 0,97 per thousand in European countries (3) and 1,15 per thousand in the United States of America (4). In the light of studies conducted in different provinces of Turkey, the frequency of neural tube defects has been found to differ between 3-5,8 per thousand (5). Sufficient amount of folic acid taken in preconception period is reported to prevent NTD development (6). Within this scope, women who are planning to get pregnant should use 400 mcg

folic acid daily starting from the planning state until the twelfth week of pregnancy (7). Due to the number of unplanned pregnancies and because of not being able to generalize folic acid use within the process; a great number of countries, especially United States of America, started compulsory folic acid enrichment programs after 1998 (8).

Individuals with high levels of education who know about neural tube defects and especially people working in health sector start using tablets containing folic acid which they get from pharmacies without consulting a doctor after they start planning on pregnancy. Even if individuals consult a physician, pregnancy and folic acid supplement are currently indispensable. Physicians have made this supplement a routine. Folic acid is started for women who plan to get pregnant or for pregnant women without checking their folic acid level. What is worse is

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women using folic acid supplement without consulting a physician. Instead of tablets which include 400 mcg folic acid, these women use tablets which include 5 mg folic acid as a result of suggestions from the environment and especially because they are cheap. As a result, they get folic acid more than 10 times of the dose recommended in pregnancy.

There are studies in literature which make an association between high doses of folic acid taken during pregnancy and autism (9-12). Autism is a neurodevelopmental disorder which courses with delays and deviations in mutual social interaction, language and communication and presence of repetitive stereotyped behaviours and interests (13).

In pregnant women, the transition of folic acid from the placenta is closely associated with mother's plasma folic acid concentration and for this transition to take place in a healthy way, mother's plasma folic acid level should be higher than 7 nmol/L (3,08 ng/ml) (14,15).

The aim of this study is to assess whether every woman in Malatya has a deficiency which requires routine use of folic acid through the folic acid levels of women who refer to health institutions.

#### MATERIAL and METHODS

This study was approved by the 2017/18-7 numbered decision of İnönü University Scientific Research and Publication Ethics Board. Our study was conducted on the records of female patients in reproductive age group (between 18 and 45) who referred to Neurology and Internal Medicine Polyclinics of Inonu University TOTM and Malatya Training and Research Hospital and whose folic acid levels were checked by the related physician between the dates January 2016 and June 2017. Women who were pregnant at the moment of referral to hospital were excluded from the study. In addition, the records were examined retrospectively and women who had malignant diseases, megaloblastic anemia, malabsorption syndrome, intestinal resection, hyperthyroid and those who were using anticonvulsant drugs were excluded from the study. These conditions have been reported to influence folic acid level in literature. Following this exclusion criteria, the study was conducted with 1003 remaining records.

IBM SPSS Statistics 22.0 for Windows package program was used for statistical analyses. Kruskal Wallis Test was conducted on the data to find out whether there were statistical differences between all groups in terms of age and folic acid values. Significance level was accepted as  $p < 0.05$ .

The media (min-max) values of the ages of women whose records were taken was found to be 23 (18-45). The women included in the study were grouped in 3 as 18-29, 30-39 and 40+ according to their ages. The distribution of women according to these three age groups is given in Table 1.

**Table 1. Women's age ranges and percentages**

Age ranges	n	%
18-29	731	72.89
30-39	200	19.94
40 +	72	7.17

The complaints of women at the time of referral were widely distributed. Referral complaints, numbers and percentages are given in Table 2.

**Table 2 Women's complaints of referral to hospital, number and percentages**

Complaints of referral to hospital	n (%)	Complaints of referral to hospital	n (%)
Headache	196 (19.54%)	Dietary counseling and surveillance	13 (1.29%)
General adult medical examination	173 (17.24%)	Polyneuropathy	12 (1.19%)
Indigestion	107 (10.66%)	Peptic ulcer	11 (1.09%)
Iron Deficiency Anemia	101 (10.06%)	Essential hypertension	8 (0.79%)
Stomachache	49 (4.88%)	Carpal tunnel syndrome	8 (0.79%)
Vertigo	49 (4.88%)	Urticaria	7 (0.69%)
Upper respiratory tract infection	39 (3.88%)	Radiculopathy	4 (0.39%)
Malaise and fatigue	38 (3.78%)	Hypoesthesia	3 (0.29%)
Reflux	37 (3.68%)	Hirsutism	2 (0.19%)
Myalgia	36 (3.58%)	Renal colic	2 (0.19%)
Gastritis	29 (2.89%)	Gastroenteritis	2 (0.19%)
Hyperlipidemia	22 (2.19%)	Rheumatism	2 (0.19%)
Syncope	21 (2.09%)	Tinnitus	1 (0.19%)
Tremor	17 (1.69%)	Optic neuritis	1 (0.19%)
Migraine	13 (1.29%)		

Serum folic acid level averages of all women whose records were taken were found to be higher than the threshold value of 3,08 ng/ml, as  $7,69 \pm 3,03$  (Table 3).

**Table 3. Serum folic acid level (SFAL) averages of all women whose records were taken**

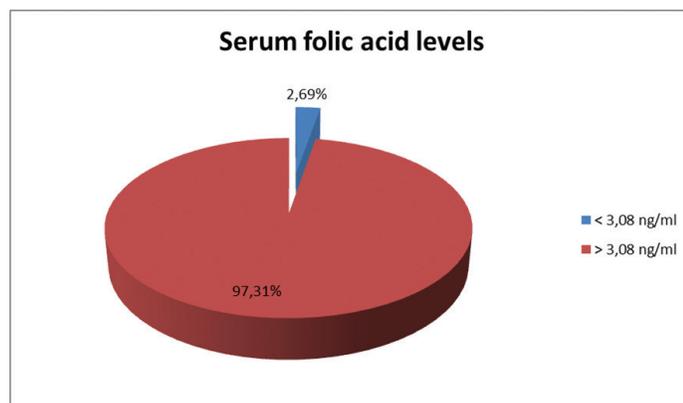
SFAL (ng/ml)Ort $\pm$ SD	n
7.69 $\pm$ 3.03	1003

When serum folic acid levels were analyzed in terms of age groups, it was found that the average serum folic acid levels is pretty higher than 3,08 ng/ml in each group and statistically significant difference was found groups in terms of age and folic acid values. ( $p < 0,05$ ). There is an increase in serum folic acid level as age increases (Table 4).

**Table 4. Women's serum folic acid level (SFAL) values according to age intervals**

Age ranges	SFAL (ng/ml) Ort ± SD	n	p
18 -29	7.44 ± 2.81	731	
30 -39	8.15 ± 3.31	200	.000
40 +	8.96 ± 3.88	72	

The serum folic acid levels of only 27 (2,69%) women whose records were taken were found to be lower than 3,08 ng/ml. Serum folic acid levels of the remaining 976 women (97,31%) were found to be higher than 3,08 ng/ml (Figure 1).



**Figure 1.** The distribution of serum folic acid levels of women whose records were taken in terms of 3,08 ng/ml, which is the lower threshold

While the serum folic acid levels of 699 (69,69%) women whose records were taken were found to have a serum folic acid level of higher than 6 ng/ml, 180 (17,94%) women were found to have a folic acid level higher than 10 ng/ml.

If these 1003 women were pregnant, they would routinely be started folic acid. However, folic acid level of a great majority (69,69%) was found to be higher than 6 ng/ml.

An individual's folic acid level differs according to environmental factors, racial characteristics, level of socioeconomical development, nutritional habits, and differences in age and gender (16,17,18). Although a great number of studies have been conducted on this issue in the world, the number of studies conducted in our country is limited. In a study they conducted on healthy individuals between the ages of 18 and 40 in Bursa in 2004, İlçöl et al. found folic acid reference interval in women as 3,53-2 ng/ml through parametric methods (19). Again, in a study they conducted with the laboratory data of 2423 women between the ages of 18 and 45 in 2006, İlçöl et al. found folic acid reference values as between 1,98-17,17 ng/ml (20). In their study they conducted on 142 women between the ages of 18 and 40, Tanyalçın et al. found folic acid reference values as between 3,9 and 18,1 ng/ml (21). As in our study, an increase was found in folic acid values as age increased in all of these three studies. In the USA, folic acid deficiency prevalence in women in reproductive

age group was 0,8%, while the average folic acid level was expressed as 11,4 ng/ml in 2006 (22). In a study conducted in Canada in 2002 on 8884 people, 63,2% of whom were women, it was found that folic deficiency rate was 0,22% (23). In a study conducted in England in 2004, borderline folic acid level was found in 8% of the women between the ages of 19 and 24, in 4% of the women between the ages of 25 and 34 (24). In a study conducted in Chile in 2003, average folic acid level of women was reported as 16,41 ng/ml (25). In Iran, in a study conducted before folic acid enrichment program, average folic acid level was found as 6 ng/ml, while folic acid deficiency rate was reported as 14,3% (26). As can be seen, studies conducted on different countries and populations have produced different results.

Calf's liver, vegetables with grain leaves such as spinach and lettuce, grains, walnut, legumes, pea, wheat, bread, banana, melon and citrus fruits are natural folic acid sources (27,28). When this list is taken into consideration, our region seems to be rich for folic acid in terms of nutritional habits. In addition, a great number of pregnancies are unplanned. When TNSA 2013 numbers are analyzed, it can be seen that the rate of planned pregnancies is 76% in our country (29). In their study they conducted in Malatya in 2004, Tekiner et al. found that 62% of births took place as a result of planned pregnancy (30). Although pregnancy is realized in the advanced stages of the first trimester in which neural tube development is completed, without use of any folic acid supplement, the rates of births with NTD is between 3-5,8 per thousand in our country (5). There is a serious difference between unplanned birth and rates of births with NTD. In the light of this information, health professionals in Turkey should work cooperatively and enable women to get sufficient amount of folic acid. Future mothers should be taught a discipline to meet their folic acid needs. In case of finding deficiencies despite all these, access to supplement drugs should be made easier and these drugs should be used in a controlled manner.

Autism, which was initially thought to result from parents' attitudes, lack of interest or worries about establishing social relations, has recently begun to be thought to have neurobiological basis rather than the upbringing of the child. While the frequency of autism was 4,4/10000 until 25 years ago (31), it has continually increased in years and became 1% in 2010 (32,33). While there is no official information, the incidence of autism is 1/150 according to information obtained from non-governmental organizations (34). In the United States of America, since 1990s when folic acid supplement began to be made on foods to protect from neural tube defects a concurrent increase has been mentioned in autism prevalence (35,36).

The purpose of the present study is not to analyze the effect mechanism of folic acid on molecular level. We also do not claim that folic acid is unnecessary. What we aim to do is just to create awareness about the unnecessary and excessive use of a molecule associated with a serious disease as autism without analyzing its level in the

pregnant woman. Our purpose is to prevent unnecessary drug usage. Excessive and long term use of supplements such as vitamins and minerals are known to have harmful effects (37). Although our study gives an idea about the folic acid level, all of the women in our study are individuals who have referred to hospital. It will be possible for us to have a more accurate opinion as a result of studies on healthy population with greater participation. In the light of this study, we believe that there is not too much folic acid deficiency due to nutritional habits in the province of Malatya and thus folic acid supplement should be made in case of necessity after checking folic acid levels.

A situation which we did not predict at the beginning and which came out with the results is the increase in folic acid level with the increase in age. We believe that this increase seen in Table 4 is associated with the fact that the young population are fed with more refined and fabricated food products when compared with the older population. It is an undeniable fact that the intake of this molecule which is abundant in green vegetables, fruit and grain decreased with fast food culture.

## CONCLUSION

We believe that physicians should start folic acid after taking into consideration the nutritional habits and socioeconomic characteristics of the region they live in and after they check serum folic acid level.

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