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ORIGINAL RESEARCH

Folic Acid Awareness and Utilization in Pregnant Women with Neural Tube Defect Risk Factors: A Prospective Cohort Study

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ABSTRACT

Our aim in our study was to evaluate folic acid use and awareness among pregnant women with NTD risk factors. The prospective cohort study encompassed singleton pregnant women in their first trimester at a tertiary hospital in Turkey. The study group consisted of 132 pregnant women with at least one NTD risk factor and equal number without any risk factors, forming the control group. Demographic data were collected via responses to a 10-question survey developed through a literature review. The survey explored participants' knowledge of folic acid and awareness of NTDs. It was conducted face to face and categorized by outcome. The high-risk group exhibited better folate awareness and use. Although there was a significant increase in pre-pregnancy folate use in the high-risk group, only 18.35% had used pre-pregnancy folate. The study showed that folate awareness was higher among participants with at least a university degree. In conclusion, despite recommendations for pre-conceptional folate use, the study reveals that awareness and use are low and emphasizes the need to increase social awareness, especially by targeting women with NTD risk factors.

Keywords: Folate. Folic Acid. High-Risk Pregnancy. Awareness. Neural Tube Defect.

Nöral Tüp Defekti Risk Faktörleri Olan Gebe Kadınlarda Folik Asit Farkındalığı ve Kullanımı: Prospektif Bir Kohort Çalışması

ÖZET

Bu çalışmayla NTD risk faktörü olan gebe kadınların folik asit kullanımı ve bilinç düzeyini değerlendirmeyi amaçladık. Üçüncü basamak bir hastanede prospektif kohort çalışması olarak tasarlanan bu çalışma, gebeliğin ilk trimesterindeki tekil gebeleri kapsıyordu. Çalışmaya risk grubunu oluşturan en az bir NTD açısından risk faktörü olan 132 gebe ve kontrol grubu olarak da risk faktörü olmayan benzer sayıda gebe kadın dahil edildi. Literatür taraması yoluyla geliştirilen 10 soruluk bir ankete verilen yanıtlara dayanan çalışmamızda beraberinde demografik veriler toplandı. Anket, katılımcıların folik asit hakkındaki bilgilerini ve NTD'lere ilişkin farkındalık düzeyini araştırdı; anketler yüz yüze gerçekleştirildi ve sonuca göre kategorize edildi. Risk grubunda olan gebelerde folat farkındalığı ve kullanımı daha yüksek bulundu. Riskli grupta gebelik öncesi folat kullanımı kontrol grubuna kıyasla yüksek bulunmasına rağmen, yalnızca %18,35'i gebelik öncesi folat kullanmıştı. Çalışma, en az üniversite diplomasına sahip katılımcılar arasında folat farkındalığının daha yüksek olduğunu gösterdi. Sonuç olarak prekonsepsiyonel folat kullanımına yönelik önerilere rağmen çalışma, farkındalık ve kullanımın düşük olduğunu ortaya koymakta ve özellikle NTD risk faktörleri olan kadınları hedef alarak toplumsal farkındalığın artırılması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Folat. Folik Asit. Yüksek Riskli Gebelik. Farkındalık. Nöral Tüp Defekti.

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Folate, also known as vitamin B9, serves as a vital cofactor in DNA and RNA synthesis, DNA methylation and neurological functions[1,2]. Methionine, an essential amino acid, is crucial for growth, development, and neural tube formation. Insufficient folate intake during pregnancy results in decreased methionine levels, leading to adverse pregnancy outcomes such as neural tube defects (NTDs) including spina bifida, anencephaly, and encephalocele[3-5]. Recognizing this, since the early 1990s, various health organizations worldwide, including the World Health Organization (WHO) and the U.S. Public Health Service, recommend daily 400 micrograms of folate supplementation from preconception to the 12th week of pregnancy[6-9]. Despite these global campaigns and guidelines, many countries still experience low folate intake during the periconceptional period[5,10,11].

Numerous risk factors have been identified for NTDs. Among them are a history of previously delivering an NTD-affected baby, a family history of NTD in either parent, pregestational diabetes, obesity, having the *MTHFR gene* mutation, and exposure to folate antagonists like valproic acid or carbamazepine, which are antiepileptic medications. Other risk factors include a history of fever or exposure to heat during the first trimester. Recognizing these risk factors is crucial for understanding and addressing the potential causes of neural tube defects[12].

Initiating folic acid supplementation in the preconception period is of heightened importance for pregnant women with risk factors for NTDs due to the increased risk. Despite this high importance, there are challenges such as low sociocultural level in the society, difficulties in accessing health services and accurate information, and lack of insurance coverage for folic acid preparations. Through this study, we aimed to assess folic acid use among pregnant women with any risk factors associated with NTDs and to investigate the level of knowledge and awareness of folic acid supplementation in these women and to assess its status compared to the general population.

Material and Method

This study was conducted with singleton pregnant women in their first trimester, aged 18-45, seeking outpatient care at the Perinatology Clinic of a tertiary education and research hospital in Istanbul, Turkey, between February 2023 and June 2023. The study adhered to the principles of the Declaration of Helsinki and received approval from thehospital's Ethics Committee (Decision date and number: 06.02.2023 - 1). Participants consisted of pregnant women with at least one identified risk factor for neural tube defects and pregnant women in the control group. The control group consisted of pregnant women without any identified risk factors and without a history of neural tube defects. Sample size was calculated at 95% confidence interval and 0.80 effect size. The study was based on responses to a 10-question survey developed through literature review[15-18]. The first three questions in the questionnaire aimed to inquire about educational level, employment status and family type, while the other seven questions aimed to inquire about folic acid use and knowledge about folic acid. Additionally, demographic information such as age, gravidity, parity, history of abortions, and pre-pregnancy body mass index of the patients were documented.

Risk factors for NTDs include a family history of neural tube defects, a history of NTD in a previous pregnancy, pregestational diabetes, obesity, antiepileptic drug use, *MTHFR gene* mutation, and a history of fever or exposure to heat (such as sauna) during the first trimester[13]. Through the provided questionnaire, the study investigated the participants' educational status, occupations, family types, whether the pregnancies were planned, their knowledge about folate as a vitamin, and their awareness of what neural tube defects entail. Additionally, to explore their awareness of folate, their knowledge about the necessity of folate supplementation starting from the preconception period, and the potential complications of folate deficiency were assessed and recorded. After measuring the participants' knowledge levels, questions regarding whether they used folate during their pregnancies, and if so, at which stage of pregnancy they started using it, were asked and noted. All these questions were posed to the participants in a face-to-face manner after obtaining informed consent. Pregnant women included in the study were further categorized based on whether they received an NTD diagnosis during follow-ups.

Statistical Analysis

In this study, statistical analyses were conducted using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software package program based in Utah, USA. The evaluation of data involved descriptive statistical methods such as mean, standard deviation, median, and interquartile range. Additionally, the Shapiro-Wilk normality test was employed to examine the distribution of variables. For variables demonstrating normal distribution, independent t-tests were utilized for the comparison of binary groups, while the Mann-Whitney U test was applied for variables with non-normally distributed data when comparing binary groups. Chi-square tests were used for comparisons involving qualitative data. The significance level for interpreting results was set at $p<0.05$.

Results

During the study period, 132 pregnant women with at least one risk factor for neural tube defects (NTDs) (the high-risk group) and 135 pregnant women without any risk factors under the same conditions (the control group) consecutively presenting to our hospital were included in the study. When the two groups were compared in terms of sociodemographic characteristics, no statistically significant differences were found in the mean age, height, parity, number of miscarriages, education level, occupation, and family status of the pregnant women (Table I). However, mean weight, BMI and gravida were significantly higher in high-risk pregnancies (76.78±18.45 vs. 72.21±12.33, p=0.018; 29.23±6.9 vs. 27.6±4.65, p=0.025; 3.14±1.68 vs. 2.52±1.54, p=0.001).

Table I. Demographic characteristics of pregnant women at risk for NTD and comparison with the control group

		Risk group n:132	Control group n:135	p
Age (year, mean±SD)		31.48±5.83	31.42±7.93	0.949*
Height (m, mean±SD)		1.62±0.07	1.62±0.06	0.675*
Weight (kg, mean±SD)		76.78±18.45	72.21±12.33	**0.018***
BMI (kg/m², mean±SD)		29.23±6.9	27.6±4.65	**0.025***
Gravida (mean±SD)		3.14±1.68	2.52±1.54	**0.001†**
Parity (mean±SD)		1.45±1.19	1,19±1,05	0.089†
Abortus (mean±SD)		0.69±1.04	0.56±0.95	0.302†
Education N (%)	Illiterate	5 (3.79)	7 (5.19)	0.115+
	Primary School	67 (50.76)	52 (38.52)	
	High School	29 (21.97)	44 (32.59)	
	University	29 (21.97)	26 (19.26)	
	Post-graduate	2 (1.52)	6 (4.44)	
Job N (%)	Not-working	100 (75.76)	100 (74.07)	0.848+
	Civil servant	10 (7.58)	12 (8.89)	
	Blue-collar	6 (4.55)	4 (2.96)	
	White-collar	16 (12.12)	19 (14.07)	
Family N (%)	Nuclear family	112 (84.85)	115 (85.19)	0.939+
	Extended family	20 (15.15)	20 (14.81)	

*Independent T-Test †Mann Whitney U test. + Chi-square test

According to the responses to the questionnaire provided to the patients, while 81 (61.36%) of pregnant women in the high-risk group knew that folic acid is a vitamin, only 10 (7.58%) had an idea about what neural tube defects were in the same group. In the control group, 78 (57.78%) pregnant women knew that folic acid is a vitamin, while 11 (8.15%) of the pregnant women in this group had an idea about neural tube defects (Table II). In this regard, when compared with the control group, the result was statistically similar. Regarding the necessity of using folic acid during pregnancy, 170 (63.67%) of all participating pregnant women were informed, and when compared with the control group, pregnant women in the high-risk group were found to be significantly more aware (95 vs. 75) (p=0.005). On the other hand, pregnant women who were knowledgeable about the possibility of folic acid deficiency causing NTDs constituted only 23.97% of all groups. Parallel to the previous question, pregnant women in the risk group were found to have a significantly higher level of knowledge about the potential of folic acid deficiency causing NTDs compared to pregnant women in the control group (Table II).

Table II. Survey questions and responses for assessing folic acid awareness and knowledge in pregnant women.

		Risk group n:132		Control group n:135		p
Is folic acid a type of vitamin?	Yes	81	61.36%	78	57.78%	0.792+
	No	12	9.09%	15	11.11%	
	No idea	39	29.55%	42	31.11%	
Do you know what neural tube defects are and how it can affect the baby?	Yes	10	7.58%	11	8.15%	0.862+
	No	122	92.42%	124	91.85%	
Do you know that folic acid use is necessary during pregnancy?	Yes	95	71.97%	75	55.56%	**0.005+**
	No	37	28.03%	60	44.44%	
Do you know that folic acid deficiency can cause neural tube defects?	Yes	41	31.06%	23	17.04%	**0.007+**
	No	91	68.94%	112	82.96%	
Did you use folic acid during your pregnancy?	Yes	110	83.33%	92	68.15%	**0.004+**
	No	22	16.67%	43	31.85%	
If you used folic acid during pregnancy, when did you start?	Preconceptional period	31	28.18%	17	18.48%	0.107+
	As soon as I found out I was pregnant	79	71.82%	75	81.52%	
For those who started folic acid as soon as they found out about their pregnancy, at what week did you find out about your pregnancy?		5.45±2.41		5.32±2.3		0.722†

+ Chi-square test, † Mann Whitney U

According to the directed questions about patients' folic acid use, 110 (83.33%) of pregnant women with risk factors used folic acid during pregnancy, and this rate is higher than the control group -92 (68.15%) of pregnant women without risk factors-, regardless of the daily folic acid dose used (p=0.004). However,

although folic acid use in the pre-conception period was statistically significantly higher in the high-risk group, only 18.35% of all pregnant women took a daily pre-conceptual dose of 400 micrograms of folic acid . In the risk group, among those who started using folic acid as soon as they learned about their pregnancy, the average week of folic acid initiation was determined as 5.45±2.41. Folic acid onset week was found to be 5.32±2.3 in the control group. (Table II). When the education levels were compared with folic acid use irrespective of the presence of risk factors, 23.8% of patients with at least a university degree used folic acid starting from the pre-conception period, while this rate was 16.2% for those without a university degree. According to these results, folic acid use and awareness are much better in those with at least a university degree compared to those without a university degree (p<0.001) (Table III).

Table III. Comparison of Folic Acid Usage in Patients Based on Educational Status.

	Not a university graduate	At least university graduate	
	n (%)	n (%)	p+
FA used as recommended	33 (16.2)	15 (23.8)	**<0.001**
FA used but not as recommended	109 (53.4)	45 (71.4)	**<0.001**
FA have not used	62 (30.4)	3 (4.8)	**<0.001**

+ Chi-square test
FA: Folic acid

Discussion and Conclusion

Folic acid is a vital vitamin during the embryological period, serving essential roles in cell division, tissue development, and hematopoiesis. Pre-conceptional folic acid use is supported by recommendations and incentive policies in many countries. Since the research by Hibbard and Smithells[19] in 1965, linking maternal folic acid intake to neural tube defects (NTDs), research aimed at increasing awareness and assessing knowledge levels remains relevant, particularly in low socioeconomic countries. In a study conducted by Yamamoto and Wada[15] in 2017, despite 70.4% of pregnant women being aware of the protective effects of folic acid, only 20.4% used it in the preconception period. Similarly, Alblowi et al.[16], in their 2018 study, found that 58.4% of surveyed women claimed to have used folic acid in previous pregnancies. However, over half of the participants had incorrect information about the timing of use, and only 4% had knowledge about the recommended dosage. Our results aligned with these findings, suggesting that our study participants in the high-risk group exhibit higher folic acid usage and knowledge levels compared to the general population.

In Turkey, several studies have assessed the knowledge and awareness of folic acid use among women of reproductive age and pregnant women. Karaçil Ermumcu et al.[17] identified a 70.2% rate of folic acid use among pregnant women. However, nearly half of the women of reproductive age included in the study had no knowledge about the need for pre-conceptional folic acid use to prevent congenital anomalies like neural tube defects. Another study by Baykan et al.[18], conducted in the central Anatolian region of Turkey at Family Health Centers, revealed that less than half of women of reproductive age (46.3%) had any knowledge about folic acid. Comparing our results with these regional studies, our findings align with the literature regarding folic acid usage frequency in pregnant women without risk factors. In particular, in the high-risk group, our study shows better adherence and higher awareness of folic acid use compared to these 2 studies in the literature that investigated awareness in the general population.

Our study was designed to investigate the awareness and utilization of folic acid among pregnant women with NTD risk factors, aiming to highlight their awareness compared to other pregnant women. The revealed proportions, both in the presence or absence of risk factors, demonstrate the significantly low prevalence of folic acid use from the preconception period onward. Among the 132 pregnant women with risk factors, 110 reported using folic acid during pregnancy, but only 31 of them, accounting for 28.18%, initiated folic acid intake during the preconception period. Out of the 5 pregnant women diagnosed with NTD during follow-ups, only 1 had started taking a low dose (400 mcg) of folic acid from the preconception period (Figure 1). The control group also exhibited a low pre-conceptional folic acid usage rate, standing at only 18.48%, emphasizing the overall inadequate adoption of pre-conceptional folic acid use in the community.

In our study, both groups had insufficient knowledge about the potential of folic acid deficiency to cause NTD. As expected, the awareness of the possibility of folic acid deficiency causing NTD was higher in the group with risk factors. Similarly, patients in the group with risk factors for NTD were found to have a higher awareness of the necessity of folic acid use throughout pregnancy compared to the control group. These patients also demonstrated greater care in using folic acid both before and during pregnancy. Despite the higher awareness and usage levels among patients with risk factors for NTD, our study's results suggest that, overall, the knowledge and awareness levels in the community are considerably low compared to the intended goals.

Although it is the first research article in the literature in terms of evaluating the awareness, use and knowledge level of folic acid in high-risk pregnant

Pregnant Women with Neural Tube Defect

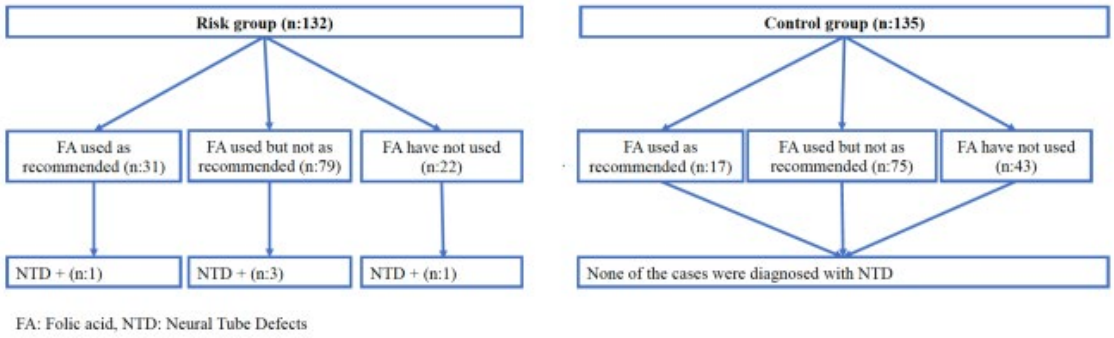

***Figure 1**:*
Folic acid usage status of patients diagnosed with neural tube defects

women in terms of NTD, it has some limitations. These include the single-center nature of the study and the relatively small number of patients. Further studies with more pregnant women will provide more generalizable results to have an idea about the community and all high-risk pregnant women in the community. A larger patient population could have been obtained by keeping the study plan longer, but we were not in a position to do this due to the intensity of our study plan. Considering the regional variation in the incidence of neural tube defects among different ethnicities and races, along with the potential influence of varying regional socioeconomic levels, we believe that multicenter studies involving larger patient groups are needed. This would contribute to a more comprehensive understanding of neural tube defects and their risk factors in diverse populations. Detailing the timing and duration of exposure to risk factors would have been more meaningful in terms of establishing a relationship. The fact that each participant was not equally exposed to certain risk factors may have affected their level of concern and awareness. Although we included the most common NTD risk factors, the study could have been expanded to include other less common risk factors.

Despite the absence of a globally determined and consensus-based folic acid dosage and initiation time for most of the mentioned risk factors, we believe that a public awareness campaign, including national-level public service announcements, promotions, and policies, should be implemented to increase awareness and promote the use of folic acid among women of reproductive age with risk factors. This initiative should involve family physicians, obstetricians and gynecologists, and all relevant healthcare professionals working in family health centers, as well as the health ministries of countries, to undertake the role of preventive medicine and contribute to enhancing awareness and usage of folic acid in women at reproductive age with risk factors.

Insufficient folic acid use and awareness during the preconception period are observed among pregnant women with risk factors for neural tube defects (NTD) in our society, particularly in Istanbul. The low rates, even in a populous metropolis, emphasize the need for prioritized efforts by health authorities to inform and facilitate access to preventive healthcare services for women with low education levels, unplanned pregnancies, and existing risk factors. In addition, the fact that folic acid awareness increases as the level of education increases emphasizes the importance of education.

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Idea and design: C.N.E., E.A.D., M.B.; Data collection and processing: C.N.E., E.A.D.; Analysis and interpretation of data: C.N.E., M.O., S.G., V.M.; Writing of significant parts of the article: C.N.E., M.B.
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