



## Adherence of Saudi women with epilepsy to folic acid intake in the preconceptional period in two tertiary care hospitals in Riyadh: A cross sectional study



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### ABSTRACT

Antiseizure medication have been associated with an increasing risk of congenital anomalies. Medical authorities recommend taking folic acid during the pre-conceptional period to reduce the risk of congenital malformations in the newborns of women with epilepsy (WWE). In this cross-sectional study, we aimed to measure the adherence of Saudi WWE to folic acid intake. We included WWE visiting outpatient epilepsy clinics in King Abdulaziz Medical City and King Fahad Medical City in Riyadh between September 2017 and August 2018. By consecutive non-probability sampling, we identified 85 patients who met the inclusion criteria of the study. The data were collected by a self-administrated questionnaire. We found that the mean age of the subjects was  $33 \pm 7.5$  years. One third were university graduates. Eighty percent were aware of the role of folic acid in preventing congenital anomalies, and 63.9% were taking it during the preconceptional period. No association was found between educational level and adherence to folic acid intake. In conclusion, adherence to folic acid intake among Saudi WWE is not optimal. More efforts are needed to increase patient adherence to folic acid intake.

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### Introduction

Epilepsy is a disorder of the brain characterized by a long-lasting predisposition to generate epileptic seizures [1]. It is one of the most prevalent neurological diseases around the world. According to a meta-analysis of international studies, the prevalence of active epilepsy is 6.38 per 1000 people. Approximately 80% of people with epilepsy live in low- and middle-income countries [2,3]. In Saudi Arabia, the prevalence of epilepsy is 6.54 per 1000 people [4].

Epilepsy is a chronic disease, so patients with epilepsy rely most of their lives on drugs, especially anti-seizure medications (ASMs). Unfortunately, maternal exposure to ASM during pregnancy is associated with an increased risk of congenital anomalies and developmental disorders in the newborns [5]. The European Registry of Antiepileptic Drugs and Pregnancy (EURAP) indicates a risk of congenital anomalies ranging from 2% for lamotrigine at doses of less than 300 mg per day to 24% for valproate at doses of more

than 1500 mg per day, establishing an association between higher ASM doses and the risk of congenital anomalies [6]. Locally, a study conducted in Saudi Arabia in 1999, representing 79 pregnancies in 44 Saudi women, showed a probability of 2.5% for a congenital malformation in Saudi women with epilepsy (WWE) using ASMs [7].

The occurrence of congenital anomalies in critical periods of organogenesis is associated with folic acid intake, as folic acid has a major role in preventing malformation and the well-being of the embryo. Inadequate folic acid intake during pregnancy is associated with intrauterine growth retardation, preterm abortions, and neural tube defects. Studies have shown that folic acid supplementation decreased the incidence of neural tube defects. In the other hand, some ASMs are associated with a reduction in folic acid; this is especially the case for barbiturates, phenytoin, and carbamazepine, which may cause a severe reduction of up to 90% in serum folate levels. Lamotrigine was developed initially as antifolate drug, although, this effect was not confirmed clinically.

Others, such as valproate, have no effect on serum levels but may affect folic acid metabolism by inhibiting metabolic enzymes [8–10]. The American Academy of Neurology (AAN) recommends folic acid supplementation in the pre-conceptional period to reduce the risk of major congenital malformations in the newborns of women with epilepsy who take ASMs [11].

Studies have shown suboptimal adherence of women with epilepsy to folic acid intake. One study conducted in China showed that 35.3% of pregnant women with epilepsy had never taken folic acid, and less than one-third of the study sample started taking folic acid before conception [12]. Another study conducted in Brazil showed an adherence rate of 42% for folate supplementation in WWE [13]. The Epilepsy Birth Control Registry (EBCR) indicated a prevalence of 46.7% for folic acid use among WWE [14]. In Saudi Arabia, several studies conducted in the general population showed poor pre-conceptional adherence to folic acid intake among Saudi women [15–17].

However, the adherence of Saudi WWE to folic acid intake is unknown. The aim of the present study was therefore to determine adherence of Saudi WWE to folic acid intake in the pre-conceptional period and to study the factors that could increase compliance with folic acid supplementation during the pre-conceptional period.

**Methods**

*Study design, area, and settings*

This cross-sectional study surveyed all female patients with epilepsy who visited outpatient epilepsy clinics between September 2017 and August 2018 in two different tertiary centers in Riyadh: King Abdulaziz Medical City - Riyadh (KAMC-R) and King Fahad Medical City (KFMC). The study was approved by the institutional review boards in both centers, and the consent form was used as the cover page of the questionnaire.

*Identification of study participants*

A consecutive non-probability sampling technique was used in the study to enroll all patients who met the inclusion criteria. The inclusion criteria of the study were Saudi women aged between 18–50 years who had been diagnosed with epilepsy by a neurologist and who had visited the epilepsy clinics in any of the study centers during the study period. Women who were not married prior to the study were excluded because out-of-wedlock births in Saudi Arabia are exceedingly rare due to religious, cultural and legal reasons.

*Data collection process*

The data were collected using a self-administered questionnaire from all patients who met the inclusion criteria. The questionnaire was developed in the English language by the research team and then translated by a certified translator to Arabic, followed by back-translation to English by another certified translator to ensure compatibility. The questionnaire was validated by three experts in the field of neurology to assess content validity. A pilot study was conducted using 24 subjects in the same study population to assess the reliability of the questionnaire and yielded a Cronbach's alpha score of 0.8. The consent forms were given to the patients by the co-investigators, who collected the data when the patients came to a routine appointment in outpatient epilepsy clinics. The data collected in this study were based on selected sociodemographic and clinical factors and the patient's folic acid supplementation status. Sociodemographic factors included

maternal age, social status, education level, and occupational status. Independent variables for the enrolled patients included the duration of epilepsy, seizure frequencies, anti-seizure medication use, and number of pregnancies. A five-point Likert scale was used to assess the outcome variable of the patient's adherence to folic acid during the pre-conceptional period.

*Data analysis*

Adherence of folic acid was estimated as the mean score of the nine items using a five-point frequency scale from never to always. A score of three or more was considered to indicate adherence to folic acid intake. Microsoft Excel 2016 was used for data entry, and IBM SPSS Statistics for Windows, Version 20.0, was used for data analysis. The categorical data, such as educational level and social status, were presented as frequencies and percentages, while numerical data, such as the number of pregnancies and age, were presented as mean and standard deviation (SD). The Chi-square test, or the Fisher exact test when appropriate, was used to assess the association of adherence (yes/no) with baseline characteristics such as educational level. A test was considered significant if the p-value was less than 0.05.

**Results**

Eighty-five women with epilepsy were studied. The age range was 18 to 50 years (mean ± SD, 33 ± 7.5). Fifty-eight (69.9%) patients lived outside Riyadh. Twenty-nine (34.1%) patients had a university degree, while 37 (43.5%) had a high school certificate as the last degree in education. Four women were pregnant for the first time during the study.

Seventy-two (84.7%) patients had been pregnant before; 57 (79.2%) of those patients had been on ASMs during their previous pregnancies. Of 72 patients who were pregnant, 50 (69.4%) had planned their pregnancies. Only 39 (45.9%) subjects reported that they had used at least one contraceptive method. There was no statistically significant correlation between the folic acid intake and use of contraception. Sixty-seven (78.8%) of the subjects had borne at least one child, and a total of 190 children were borne by them. Only 1 child (0.5%) had a congenital anomaly in the form of a cleft palate. The duration of epilepsy among the subjects was 10 ± 6.5 years. Sixty-eight (80.0%) patients experienced more than 3 seizures in their lifetime [Table 1].

Seventy-nine (92.9%) subjects had heard about folic acid, and 68 (80.0%) were aware of the importance of folic acid in preventing congenital anomalies. Sixty-eight (80%) subjects were aware that women with epilepsy needed more folic acid than was required

**Table 1**  
Sociodemographic and Clinical Variables.

		N	%
Social Status	Married	78	91.80%
	Divorced	5	05.90%
	Widowed	2	02.40%
Occupational Status*	Unemployed	67	79.80%
	Employed	17	20.20%
Number of Antiseizure Medications	None	2	02.40%
	Monotherapy	52	61.20%
	Polytherapy	31	36.50%
Number of Seizure in lifetime	One to Three	17	20.00%
	More than Three	68	80.00%
Dosage of Folic Acid	1 mg	11	12.94%
	5 mg	40	47.05%
	Dosage Unknown	34	40.00%

\* Missing one value.

**Table 2**  
Folic Acid Supplementation.

		N	%
Know about Folic Acid from:	Media	11	13.40%
	Relatives	20	24.40%
	Physician	75	91.50%
Prescribed Folic Acid by:	Neurologist	46	56.10%
	OBGYN	52	63.40%
	Family Physician	2	02.40%
	Pharmacist	1	01.20%
	Never Prescribed	2	02.40%

\* Patient can select more than one option.

by the general population. Only 46 (56.1%) of all the subjects were taking folic acid at the time of the study [Table 2].

A total of 76 women were pregnant before or during the study. Fifty-nine (77.6%) of them were adherent to a folic acid intake. Only 46 (63.9%) were taking folic acid for the three months before pregnancy. Table 3 shows the association between the sociodemographic variables, including age, social status, educational level, and occupational status, and adherence to folic acid intake.

**Discussion**

Approximately two-thirds of Saudi WWE were adherent to folic acid intake in the preconceptional period, and more than three-quarters of them were generally adherent to folic acid. By contrast, in previous studies, the adherence rate for folic acid intake in the preconceptional period among women in Saudi Arabia ranged from 4 to 22% [15–17]. Also, another study done in Qatar and Oman showed low adherence rate to folic acid in the preconceptional period [18]. This disparity in the results between our study and previous studies in the same country possibly reflects a greater concern among women with epilepsy regarding congenital anomalies that are linked to ASMs and therefore a greater motivation for compliance with folic acid intake. However, the adherence rate in our cohort was also higher than the reported rate in international studies done in China (29.1%) and Brazil (42.4%) among WWE [12,13]. Because the sample came from tertiary medical centers and the subjects were followed in specialized epilepsy clinics, sampling bias might have contributed to this relatively high adherence rate.

Most of our study subjects (80%) were aware of the role of folic acid in preventing congenital anomalies, and this result is comparable to results of a recent study done in 2018 among Saudi women [19]. Nevertheless, the awareness of Saudi WWE regarding the role of folic acid was higher in our cohort than in Saudi women studied in 2012 and 2013 [15,20]. This difference could indicate an

increased awareness in the last few years among Saudi women, or it may simply be due to random variation between studies conducted at different centers. However, physicians played an important role as a source of information about folic acid, as more than 90% of the subjects in our study heard about folic acid from their physicians. A similar finding was noted in another local study and suggests that the time allocated for patient education during clinical visits is an important factor for increasing awareness [19].

We found no association between educational level and adherence to folic acid intake. By contrast, previous studies done in Brazil and China showed evidence of an association between educational level and adherence to folic acid. The absence of an association in our study is possibly due to its small sample size, and the important educational role played by the physicians might have offset the education level effect.

The use of ASMs has a risk of causing congenital anomalies. In this study, we found only one child (0.5%) with a congenital anomaly that could be attributed to ASM, and this frequency was lower than expected, based on previous local and international studies [7,21]. This apparently low incidence of congenital anomalies can be attributed to two factors: the selection bias of the study sample and the fact that more than 20% of the subjects had not been on ASM in their previous pregnancies.

In addition to the intrinsic shortcomings of survey research, our study has several other limitations. The participants were selected from a convenience sample, which could introduce a selective bias. Likewise, our sampling frame may not represent the target population, as we took the sample from two tertiary centers from the capital city, where the social and economic status of its inhabitants are expected to differ from other regions. The study is also underpowered because of its small sample size in terms of finding a significant association between adherence to folic acid intake and demographic factors.

In conclusion, this study showed suboptimal adherence to folic acid intake and awareness of its significance among Saudi WWE. Establishing a national registry of antiseizure medications and pregnancy or participation by national medical centers in an international established registry will help in conducting high-quality prospective observational studies that will avoid the shortcomings of small underpowered studies.

**Ethical statement**

The study was approved by the institutional review boards in King Abdullah International Medical Research Center and King Fahad Medical cit and the consent form was used as the cover page of the questionnaire.

**Table 3**  
Association of the Adherence to Folic Acid Intake in the preconceptional period and Sociodemographic Variable.

		Adherence to folic acid intake				P-value
		Not adherent to folic acid intake		Adherent to folic acid intake		
		N = 17	%	N = 59	%	
Age*	Less than 30 years	3	13.6%	19	86.4%	0.37
	Between 30 and 39 years	6	18.2%	27	81.8%	
	More than 39 years	4	33.3%	8	66.7%	
Social Status	Married	15	21.1%	56	78.9%	0.33
	Unmarried	2	40.0%	3	60.0%	
Education Level	Less than High School	4	22.2%	14	77.8%	0.76
	High School	6	18.8%	26	81.2%	
	University	7	26.9%	19	73.1%	
Occupational Status*	Unemployed	15	24.6%	46	75.4%	0.41
	Employed	2	14.3%	12	85.7%	

\*Varibales with some missing values.

## Conflict of interest

We have no conflict of interest

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