

# Preconceptional Intake of Folic Acid Supplementation and its Associated Factors: A Cross Sectional Study on the Lebanese Females of Reproductive Age

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## Abstract

**Objective:** Infertility is recognized as a public health issue worldwide where the total fertility rate is decreasing in most countries. Hence, this study assesses the use of folic acid supplementation prior to pregnancy in the Lebanese population.

**Methods:** It was a cross-sectional study that took place between December 2019 and February 2020 using a representative sample of community patients. Of 1000 participants who were approached, 980 were completed and collected back and 953 samples were accepted. The sample was drawn from the districts of all Lebanese governorates (Beirut, Mount Lebanon, North Lebanon, South Lebanon, and Bekaa).

**Results:** Females with prior delivery of children were significantly associated with higher intake of folic acid prior to pregnancy, whereas females with low monthly income were significantly associated with lower intake of folic acid.

**Conclusion:** The findings of this study about the assessment of the use of folic acid prior to pregnancy may be the first step towards the development of efficient health promotion programs oriented for the adequate utilization of folic acid use among Lebanese population.

**Keywords:** Fertility • Preconception • Folic acid

## Introduction

Infertility is defined as the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year [1]. According to a survey between 1990 and 2004, one in every four couples in developing countries is a victim of infertility [2]. A further World Health Organization (WHO) study showed that the strain of infertility has remained the same in approximate levels in 190 countries throughout South Asia and Sub-Saharan Africa [3].

Infertility is engendered by multiple factors which include inadequate ovulation, utero-tubal- peritoneal factors, endometriosis, defective sperm quantity and quality, genital infections, trauma, surgeries, gene dysfunctions, and toxic substances, etc. [4]. In addition to the mentioned factors, unbalanced diet also plays a vital role in infertility occurrence [5]. Micronutrient status is a modifiable risk factor since essential vitamins and minerals have important roles in the physiological processes that are involved in achieving and maintaining fertility [6]. In women who are diagnosed as infertile as, lower than recommended levels of certain micronutrients have been reported since maintenance of adequate levels of micronutrients are important for oocyte quality, maturation, fertilization, and implantation. The requirement of a balanced diet is even required in women of childbearing age and is not restricted to certain age limits [6]. From the vitamins, folate (vitamin B9) is an essential nutrient that is required for DNA replication and acts as a substrate for a range of enzymatic reactions involved in amino acid synthesis and vitamin metabolism [6]. The demands for folate increase during pregnancy because it's required for growth and development of the fetus and folate deficiency prior to conception has been associated with abnormalities in both mothers (anemia, peripheral neuropathy) and fetuses

(congenital abnormalities) [7]. Current US recommendations state that a dose of 5 mg folic acid daily prior to conception required for high risk women defined as a personal or family history of neural tube defects (NTD), and females who are on anticonvulsant medications [7]. A dose of 1 mg folic acid daily for at least 2 to 3 months prior to conception and continued throughout pregnancy, and during the postpartum period is implemented for all reproductive aged women.

Infertility is recognized by the WHO as a public health issue worldwide and is an emerging disorder in many countries where the total fertility rate has decreased from 7.7 in 1966 to 6.3 in 1976 [8], and since there is lack of infertility data in Lebanon, this research aims to assess the use of folic acid supplementation prior to pregnancy in the Lebanese population [9].

## Methods

### Study design and study population

This was a cross-sectional multi-centered study conducted between December 2019 and February 2020 in community settings from all Lebanese districts. The study protocol was reviewed and approved by the Institutional Review Board of the School of Pharmacy at the Lebanese International University. A verbal informed consent was obtained from all participants prior to enrollment. The investigators assured to the participants that their privacy will be respected and the results will be presented anonymously.

### Inclusion and exclusion criteria

Eligible participants were Lebanese adults married females and

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patients with menopause were excluded.

### Sample size calculation

Based on a 50% expected frequency of infertility in the UAE women [10] and in the absence of similar studies in Lebanon, the minimal sample size calculated according to the Epi Info software version 7.2 (population survey) was 384 participants to ensure a confidence level of 95%. Of 1000 participants who were approached, 980 (98%) accepted to participate. The nonresponse rate was 2%.

### Study outcomes

The primary outcome was to assess the frequency of the intake of folic acid supplementation prior to pregnancy.

### Study procedure

Data collection was collected by a questionnaire adopted from English and translated into the Arabic language [11–13]. The interviewers filled the corresponding answers in a process that lasted for 10–20 minutes. The survey consisted of 4 sections to be filled. The questionnaire consisted of both open-ended and closed-ended questions. The questionnaire began by asking about the patient's demographic details; including age, weight, height, marriage duration, marital quality with answer options positive or negative indicating whether the female is satisfied with her relationship or not, cigarette, water-pipe and alcohol consumption, physical activity indication if the female is regularly active or not included the frequency (number of days per week) (using the self-report activity diaries), socioeconomic status categorized according to the monthly income: low ( $\leq$  400 \$), medium ( $\approx$  1500 \$), and high status ( $\geq$  6500 \$). Also, a detailed assessment of exposure to radioactive substances, and self-perceived stress assessed according to Perceived Stress Scale (PSS). PSS was developed to measure how controllable and unpredictable people viewed their lives which is an important component of the experience of stress scale with an average from 0 to 10 with 2 options  $\leq$  5 (low to intermediate stress level) or  $>$ 5 (high stress level) [14]. In addition, evaluation of family fertility problems, kinship to spouse menstrual average cycle and blood volume, and physical activity were documented. The questionnaire also pinpointed the previous history of delivery. Finally participants were asked about the intake of folic acid before pregnancy with specifying the period and dose.

### Statistical analysis

Statistical analysis was performed using IBM SPSS (Statistical Package for Social Sciences), version 20. All continuous variables were presented as Mean (M) and Standard Deviation (SD), and the categorical variables were presented as frequencies. Correlations between dietary factors and health outcomes were determined by the Pearson chi-square test; if the cell count was below 5, the Fisher's exact test was applied. Multiple logistic regressions models were used to assess the correlation between folic acid intake and the following independent variables: exposure to toxic radioactive substances, monthly income, family fertility problem, and delivery of children that showed a  $P < 0.2$  in the bivariate analysis. Potential confounders may be eliminated only if  $P > 0.2$ , in order to protect against residual confounding. Adjusted odds ratios (ORa) were then calculated and  $p$ -value  $< 0.05$  was considered statistically significant.

## Results

### Socio demographic characteristics

In our study out of 1000 questionnaires distributed, 980 (98.0%) females were enrolled in this study with a mean age of  $34.8 \pm 8$  years. There were 953 married females with a mean age upon marriage of  $25.7 \pm 4.7$  years. Around 52.5% of the patients had normal weight with  $BMI < 25$  kg/m<sup>2</sup>. Table 1 summarizes the socio-demographic factors. The results showed that our sample were mainly physically inactive 59.9%, had good relation with their husbands 93.2%, most were current smokers 25.5%, and non-alcoholic

88.1%. There were missing values in our results since not all questions were answered by all participants (Table 1).

**Table 1.** Socio-demographic characteristics.

Characteristics	N (percentage)
Age upon marriage years (Mean $\pm$ SD)	25.7 $\pm$ 4.7
Current age years (Mean $\pm$ SD)	34.8 $\pm$ 8.0
Body mass index (BMI) (Kg/m <sup>2</sup> )	
Normal weight (<25)	500 (52.5%)
Over-weight (25-30)	336 (35.3%)
Obese (>30)	117 (12.3%)
Marriage duration years (Mean $\pm$ SD)	7.0 $\pm$ 4.4
Marital quality	
positive	888 (93.2%)
negative	64 (6.7%)
Alcohol consumption	
Non-alcoholism	840 (88.1%)
Current alcohol intake	95 (10%)
Ex- alcohol	18 (1.9%)
Waterpipe smoking	
Non-smoker	793 (83.2%)
Current smoker	142 (14.9%)
Ex- smoker	18 (1.9%)
Physical activity	
Physical inactive	571 (59.9%)
Physical active	382 (40.1%)
Educational level	
Primary school or below	55 (5.8%)
Middle school	115 (12.1%)
High school	180 (18.9%)
College and above	603 (63.3%)
Employment	
Employee	587 (61.6%)
Unemployed	366 (38.4%)
Monthly income	
Low	107 (11.2%)
Medium	728 (76.4%)
High	118 (12.4%)
Toxic exposure to radioactive substances	
Yes	56 (5.9%)
No	897 (94.1%)

Menstrual blood volume	
Heavy	132 (13.9%)
Moderate	665 (69.8%)
Light	136 (14.3%)
Average menstrual cycle	
Irregular (36 days or longer)	151 (15.8%)
Short (26 days or less)	138 (14.5%)
Regular (27-35 days)	643 (67.5%)
Self-perceived stress	
≤ 5	494 (51.8%)
>5	454 (47.6%)
Kinship to spouse	
Not related	729 (76.5%)
Related	251 (22.5%)
Family fertility problems	
Yes	164 (17.2%)
No	787 (82.6%)
Having children	
Yes	542 (56.9%)
No	409 (42.9%)
Intake of folic acid 3 months before pregnancy	
No	831 (87.2%)
Yes	106 (11.1%)
Taking folic acid as supplement	
Before pregnancy	140 (14.7%)
During pregnancy	307 (32.2%)
Before and during pregnancy	166 (17.4%)
You didn't take at all	335 (35.2%)
Dose of folic acid supplement per day	
400 mcg	113 (11.9%)
500 mcg	97 (9.7%)
600 mcg	217 (22.8%)
5 mg	

## Bivariate analysis

**Association between the folic acid intake and the different variables:** Bivariate analysis showed that a significantly higher proportion of females with high income consumed more folic acid before pregnancy compared to low income 13.9% versus 8.8% with a p-value 0.002. Consumption of folic acid before pregnancy was significantly higher in females with a negative family history of infertility problems compared to positive history (85.2% vs. 14.8%) with a p-value of 0.015. A significantly higher intake of folic acid was documented in females with children compared to not having children 72.2 versus 27.6 respectively with a p-value of >0.001 (Table 2).

**Table 1.** Socio-demographic characteristics.

**Table 2.** Bivariate analysis of folic acid intake and its association with other variables.

Variables	Folic acid before pregnancy		P value
	Taken	Not taken	
BMI			
Normal	333 (54.3%)	164 (49.0%)	0.53
Overweight	217 (35.4%)	117 (34.9%)	
obese	63 (10.3%)	54 (16.1%)	
Marital relation			
Good	575 (93.8%)	308 (92.2%)	0.347
Bad	38 (6.2%)	26 (7.8%)	
Cigarette smoking			
Non smoker	431 (70.3%)	227 (67.8%)	0.609
Current smoker	153 (25.0%)	68 (26.3%)	
Ex-smoker	29 (4.7%)	20 (6.0%)	
Alcohol consumption			
Non-alcoholism	544 (88.7%)	292 (87.2%)	0.684
Current alcohol intake	57 (9.3%)	37 (11.0%)	
Ex- alcohol	12 (2.0%)	6 (1.8%)	
Waterpipe smoking			
Non-smoker	97 (15.8%)	45 (13.4%)	0.469
Current smoker	13 (2.1%)	5 (1.5%)	
Ex- smoker			
Physical activity			
Physical active	242 (39.5%)	137 (40.9%)	0.678
Physical inactive	371 (60.5%)	198 (59.1%)	
Employment			
Employee	373 (60.8%)	209 (62.4%)	0.676
Unemployed	240 (39.2%)	126 (37.6%)	
Education level			
Primary school or below Middle school	32 (5.2%)	22 (6.6%)	0.274
High school	70 (11.4%)	44 (13.1%)	
College and above	126 (20.6%)	53 (15.8%)	

**Multivariate logistic regression:** A multivariate logistic regression analysis had shown a correlation between folic acid intake and the following independent variables: toxic exposure to radioactive substances, monthly income, family fertility problems, having children. The logistic regression, taking each significant factors as independent variables, showed that toxic exposure to radioactive substances (ORa=0.64), low monthly income (ORa=0.52), and presence of positive family fertility problems (ORa=0.80)

were associated with lower intake of folic acid intake. However, having females with prior delivery of children (ORa=6.24) were significantly associated with higher odds of folic acid intake (Table 3).

**Table 3.** BMultivariate analysis. Logistic regression taking the intake vs. non intake of folic acid as the dependent variable and monthly income, presence of family fertility problems and having children before as independent variables.

Variable	P value	ORa	95% confidence interval	
Exposure to radioactive substances (Yes versus No)	0.176	0.649	0.348	1.214
Monthly income (low versus medium)	0.005	0.523	0.333	0.822
Family fertility problems (Yes versus No)	0.256	0.801	0.545	1.175
Delivery of prior children (Yes versus No)	<0.001	6.248	4.64	8.413

## Clinical Manifestations of Psychosis

Psychosis is a state of serious disconnection between personal experience and reality or loss of self-boundaries. It is mainly manifested in the existence of hallucinations and delusions. Psychosis is a hallmark or defined symptom of schizophrenia spectrum and other mental disorders, and it is related to the characteristics of other mental and behavioral disorders. The systemic inflammation and neuroinflammatory changes are related to the massive increased brain pro-inflammatory molecules, glial reactivity, neurochemical landscape alternation, and pathological remodeling of neural networks. These organic changes are accompanied by environmental stress and promote the pathological disorder of neuropsychiatry.

Psychosis can be considered to be a set of symptoms, and there are a variety of manifestations in COVID-19 patients, ranging from insomnia and anxiety to psychiatric symptoms and aggressive behavior. This pattern of psychiatric symptoms is similar to those of patients infected with SARS in previous studies, ranging from mild mental problems (such as anger, anxiety, and depressive reactions) to severe psychotic problems such as hallucinations and mania [75, 76]. A study shows that the most common mental symptoms of COVID-19 patients on admission are insomnia, followed by aggressive behavior, delusions, and severe anxiety [77]. Besides, it is characterized by depression [78], substance-related and addiction disorders [79], eating disorders, schizophrenia [15], reactive psychosis, panic attacks, OCD, post-traumatic stress disorder, agoraphobia, and other psychiatric disorders.

## Discussion

In this cross-sectional study, we present findings of major socio-demographic variables of large sample of Lebanese married females. We highlighted that females with toxic exposure to radioactive substances, low monthly income, and positive family fertility problems were associated with lower intake of folic acid intake. However, having females with prior delivery of children were significantly associated with higher odds of folic acid intake.

With the present study we can say that 17.5% of The folic acid intake variance is influenced by these factors where as there is others factors influencing the folic acid intake .this suggest that despite our inclusion of 4 independent variables in this study there is many other factors are still influencing the folic acid intake.

### Monthly income and folic acid intake

Our findings highlight that females with low monthly income have a lower folic acid intake than medium income status which is consistent with the findings of previous studies that have shown that adults with poor socioeconomic status have higher prevalence of micronutrient

inadequacies from diet and supplements [15]. Thus, compliance with federal nutrition recommendations is especially problematic among the low income populations probably due to the low level of awareness about the recommended intake of minerals and vitamins or limited capacity to afford supplements.

Folic acid supplementation prior to pregnancy has been encouraged by many countries all over the world through increasing the awareness about the intake of a balanced diet fortified with folic acid and the intake of supplements that been hindered by people in the low socioeconomic status [16].

### Family fertility problem and folic acid intake

Folic acid intake prior to pregnancy is low in females with positive family fertility problems, which is consistent with the results of other studies [17,18]. In fact, several gene variations are involved in family fertility problems which cause folate–metabolizing gene polymorphisms altering the folate metabolism pathway that accounted for infertility in women with an otherwise unspecified reason [18]. Folate deficiency increases susceptibility for hyper-homocysteinemia leading to apoptosis and further follicular atresia [19]. Thus, knowledge of defective folate genetic background could facilitate prompt identification and treatment of women trying to achieve pregnancy.

### Exposure to radioactive substances and folic acid intake

Our findings highlighted that females exposed to toxic radioactive substances have lower odds of folic acid intake prior to pregnancy which can be explained by the low level of awareness about the protective role of folic acid as antioxidant and free radical scavenger among females exposed to radioactive substances [20]. Based on other studies, folic acid intake protects from the toxicity of radioactive materials and its deficiency increases the sensitivity to radiation-induced chromosome breakage and increases the risk of infertility [21]. In addition, the effect of accidental, occupational, or therapeutic exposure to radiation may be significantly modulated by folate status which varies greatly among individuals [22,23]. While long-term research should be done to establish the clinical value of adding folic acid supplementation in the regimen of people exposed to radioactive substances.

### Delivery of prior children and folic acid intake

Our study showed that females with prior deliver of children is significantly associated with higher intake of folic acid which is consistent with the results of other conducted studies that concluded a positive association between higher intake of folic acid intake among females with prior delivery [24,25]. The findings can be explained that pre-conceptional supplementation with folic acid can be missed mainly in the first pregnancy more than in multiple pregnancies due to the fact that females awareness by the physicians about the recommended supplements will be higher in the second pregnancy [25,26]. In addition, the evidence shows that women awareness and knowledge about folic acid benefits increase after they had given birth to a child compared with those who have not had a child [24].

## Conclusion

This study provides valuable information about the use of folic acid prior to pregnancy and its correlates. The findings highlight that women from low socioeconomic classes are less likely to consume folic acid supplementation prior to pregnancy and females with prior delivery of children are significantly associated with higher intake of folic acid prior to pregnancy. The results stress on the importance of increasing awareness among females about the use of folic acid supplementation prior to pregnancy.

## Limitations

Our survey had methodological strengths and limitations. A large number of participants randomized from all Lebanese geographic areas is

an important parameter. Nonetheless, our analysis has several unavoidable limitations. The first one is the small number of included articles despite our best efforts to retrieve all related data but there is a lack of similar studies. Additionally our findings may include the use of self-reported dietary supplements intake data to estimate folic acid intake and participant's recall of past act might be a source of bias. Nevertheless, prospective studies are needed to consolidate the relationship between infertility and folic acid intake to better understand the effect of this supplementation on healthy women trying to conceive. Finally, we did not take all confounding factors into account, like the absence of other micronutrients and vitamins having an important role in reducing fertility added to the factors related to pollution; studies that include these effects into account are suggested to further refine the associations we found here.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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