



Relationship between Folic Acid and Both Anxiety and Depression During Pregnancy

Ali S. Chobok¹, Salam W. Ahjel¹ and Saif M. Hassan^{1,*}

¹Department of Pharmacy, Al-Zahrawi University College, Karbala, Iraq

Corresponding author: Saif M. Hassan (e-mail: saif@g.alzahu.edu.iq).

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Abstract: Depression and anxiety often coexist during pregnancy, potentially increasing the risk of adverse delivery outcomes like preterm birth and low birth weight. However, our understanding of the frequency, patterns, and factors influencing comorbid anxiety and depression is limited, especially in low- and middle-income countries. This study aims to: (1) explore the prevalence and patterns of prenatal anxiety and depressive symptoms among pregnant women in the mild-to-severe and moderate-to-severe categories; (2) examine the prevalence and patterns of antenatal anxiety and depressive symptoms among pregnant women in the mild-to-severe category; (3) investigate the association between frequent folic acid use and prenatal anxiety and depression symptoms. The study adopted a retrospective cohort approach and enrolled a diverse sample of 500 pregnant women receiving care at the Women and Children's Hospital in various locations across the center and south of Iraq. Results indicated that women who did not consume folic acid during pregnancy exhibited higher rates of comorbid anxiety and depression. Specifically, this pattern was observed among women in the age range of 20 to 29 years, those with a university degree, and those who had more than two previous children.

Key Words: depression; anxiety; folic acid; pregnant women; first trimester

I. BACKGROUND

According to years lived with disability, depression is the second most prevalent yet highly debilitating psychiatric condition globally [1]. It carries significant individual and socioeconomic burdens, and is associated with increased morbidity and mortality [2]. Trend analyses indicate a growing prevalence, highlighting the expanding global public health burden. Despite advancements in medication and increased understanding of biological, clinical, and imaging aspects, clinical outcomes remain diverse and dependent on both the patient and treatment approach [3].

Anxiety, characterized by distress, impending danger, and fear, constitutes the core components of this condition. When anxiety is triggered by an actual, objective factor, it is considered physiological. Pathological anxiety, on the other hand, lacks valid reasons for its persistence [4]. While anxiety can be a normal psychological response to the onset of a physical illness, it can also escalate into a symptom with pathological significance or even develop into a mental disorder. Indeed, individuals dealing with medical illnesses often experience heightened levels of anxiety [5], with generalized anxiety disorder being the most common disorder encountered in primary care settings (10.3%) [6]. Anxiety can influence

patient interactions, particularly with medical and nursing staff, and influence their perception of the disease process.

The perinatal use of folic acid supplements reduces the occurrence and recurrence of initial neural tube defects [7]. In communities where poor pregnancy outcomes are linked to inadequate dietary intake of folic acid and other vitamins and minerals, continued folate consumption post-neural tube closure may be necessary to mitigate further negative pregnancy outcomes [8]. Folate is pivotal for embryogenesis and embryonic development due to its role in DNA synthesis, a process crucial for cell division proliferation [9]. Inadequate dietary folate intake or increased metabolic requirements due to specific genetic anomalies can both lead to folic acid deficiency [10]. Lower circulating folic acid levels during pregnancy are associated with heightened risks of preterm birth, low birth weight, and delayed fetal growth. Folic acid deficiency leads to elevated blood homocysteine levels, which have been linked to habitual spontaneous abortion and pregnancy complications like placental abruption and pre-eclampsia, thereby increasing the risk of adverse pregnancy outcomes, low birth weight, and gestational term [11], [12]. Folic acid metabolism anomalies can lead to pregnancy delays and complications, highlighting the significance of

proper folate intake during pregnancy [13].

II. AIM OF THE STUDY

The aim of this study is to investigate the relationship between anxiety disorders and depression with the use of folic acid during the first trimester of pregnancy.

III. METHODS

STUDY DESIGN

This study employs a retrospective cohort design in the center and south of Iraq. From September to December 2022, a cross-sectional survey-based study was conducted to examine the prevalence of sadness and anxiety among women who experienced childbirth during the first trimester while utilizing various folic acid prescriptions.

INSTRUMENTS AND MEASUREMENTS

A questionnaire consisting of three parts was administered to gather face-to-face information from the participants. The first segment of the survey focused on background demographic information, including age, level of education, chronic diseases, number of live children, and folic acid tablet usage methods. The second component utilized the Generalized Anxiety Disorder (GAD-7) scale and the Patient Health Questionnaire (PHQ)-9, both of which have been validated [14]. GAD-7 comprises seven items and a 4-point Likert scale. Each item is assigned a score ranging from 0 to 3, yielding a total score that can range from 0 to 21. Scores of 5 to 9 represent mild anxiety, 10 to 14 indicate moderate anxiety, and 15 to 21 signify severe anxiety. PHQ-9 is a 9-item assessment with a 4-point Likert scale. The total score varies from 0 to 27, with each item being assigned a value between 0 and 3. Scores of 0-4 suggest minimal depression, 5-9 imply mild depression, 10-14 indicate moderate depression, 15-19 represent moderately severe depression, and 20-27 correspond to severe depression.

STATISTICAL ANALYSIS

The sample size was determined using the formula: $sample\ size = Z_{1-\alpha/2}^2 \times P(1 - P)/d^2$, ensuring 80% power and a 95% confidence interval. The statistical package for social sciences (SPSS® version 26, IBM Inc., Chicago, IL, USA) was employed for data analysis. Numerical variables were expressed using mean and standard deviation. When the Kolmogorov-Smirnov test indicated a non-normal distribution, the Kruskal-Wallis test was used to assess mean differences between groups. Bivariate correlation analysis was conducted to explore the relationship between clinical factors and folic acid or vitamin B12 levels. Statistical significance was determined at $P < 0.05$.

IV. RESULTS

PARTICIPANTS' GENERAL FEATURES

A total of 500 pregnant women were included in this study. The results indicated a highly significant difference ($p < 0.05$) in the age distribution of participants, with 53.4%

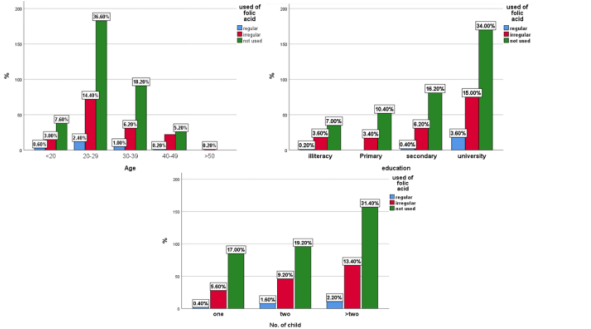


FIGURE 1: relationship between Participants features vs folic acid used

($SD = 0.81$) falling within the 20-29 years age range. Similarly, a significant difference ($p < 0.05$) was observed in the distribution of educational levels, with 52.6% ($SD = 1.0$) of participants having a university education. Conversely, 67.6% ($SD = 0.56$) of participants did not use folic acid during pregnancy, which was highly significant ($p < 0.05$) compared to other usage patterns. Among the mothers, more than 65% experienced severe anxiety based on the assessment, while 43.0% suffered from moderately severe depression (Table 1).

RELATIONSHIP BETWEEN PARTICIPANT FEATURES AND USE OF FOLIC ACID

In terms of age, 338 (67.6%) of the pregnant women did not use folic acid, which was found to be highly significant ($p < 0.05$) compared to regular use by 21 (4.2%) and irregular use by 141 (28.2%) of participants. Among them, 267 (53.4%) were in the age range of 20-29 years old, and 183 (36.6%) were aged 30-39 years. Regarding education, a significant difference ($p < 0.05$) was observed between women who did not use folic acid (170, 34.0%) and those who irregularly used it (18, 3.6%), as well as those who used it regularly (75, 15.0%). Furthermore, based on the number of children, 235 (47.0%) of the pregnant women had more than two children, and among them, 157 (31.4%) did not use folic acid (Table 2 and Figure 1).

CORRELATION BETWEEN ANXIETY AND FOLIC ACID USE

Our findings revealed a negative correlation between the use of folic acid and the incidence of both anxiety ($r = -0.642$) and depression ($r = -0.244$). Furthermore, we identified a significant correlation ($p < 0.05$) between the use of folic acid and anxiety, as well as a significant difference ($p < 0.05$) in folic acid use with respect to depression (see Table 3 and Figures 2 and 3).

RELATIONSHIP BETWEEN MOOD AND FOLIC ACID USE

The association between anxiety levels in pregnant women who did not use folic acid, based on the JAD-7 and Depression (PHQ-9) scores, and different usage practices was

Variance	Sub-variance	N	%	Mean ± SD	X2
Age	<20	56	11.2%	2.34 ± 0.81	0.021
	20-29	267	53.4%		
	30-39	127	25.4%		
	40-49	49	9.8%		
	>50	1	0.2%		
No. of life child	one	115	23.0%	2.24 ± 0.80	0.265
	two	150	30.0%		
	>two	235	47.0%		
Education	illiteracy	54	10.8%	3.17 ± 1.0	0.024
	Primary	69	13.8%		
	secondary	114	22.8%		
	university	263	52.6%		
Folic acid used	regular	21	4.2%	2.63 ± 0.56	0.02
	irregular	141	28.2%		
	not use	338	67.6%		
Anxiety (GAD-7)	mild anxiety	54	10.8%	2.47 ± 0.68	0.000
	moderate anxiety	157	31.4%		
	severe anxiety	289	57.8%		
Depression (PHQ-9)	mild depression	14	2.8%	2.91 ± 0.80	0.000
	moderate depression	144	28.8%		
	moderate severe depression	215	43.0%		
	severe depression	127	25.4%		

TABLE 1: Characteristics of study participants and percentage of each variance

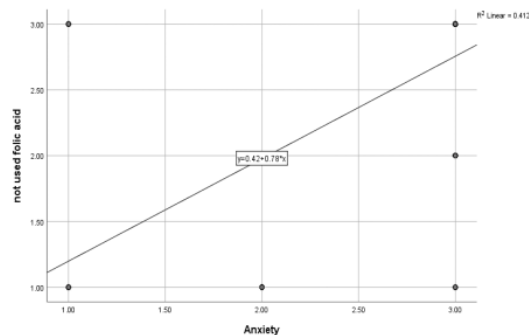


FIGURE 2: Pearson correlation between not used folic acid with parents’ GAD7

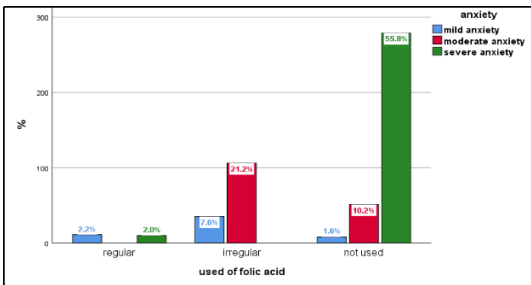


FIGURE 4: relationship between anxiety and folic acid used

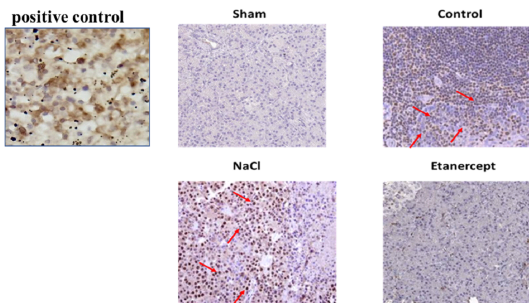


FIGURE 3: Pearson correlation between not used folic acid and score of PHQ9

examined using the Chi-square test. A significant difference ($p < 0.05$) was found between folic acid use and the severity of anxiety. Specifically, among pregnant women who did not use folic acid, more than half (67%) experienced severe anxiety. Additionally, 28.2% of pregnant women who reported moderate anxiety were irregular users of folic acid. Conversely, 4.2% of those who regularly used folic acid

exhibited mild anxiety (see Table 4 and Figure 4). We also identified a significant difference ($p < 0.05$) between folic acid use and the severity of depression. Notably, 62.60% of pregnant women who did not use folic acid experienced depression. Of those who irregularly used folic acid, 33.2% reported depression, while 4.2% of regular users experienced depression. Among those who had moderate severe depression, 43.0% were not using folic acid. Moreover, 28.8% of pregnant women with moderate depression and 25.4% with severe depression were not using folic acid. Notably, among those with severe depression, 21.2% did not use folic acid (see Table 5 and Figure 5).

V. DISCUSSION

Our study suggests that regular folic acid use during the first trimester can help reduce the risk of anxiety and depression during pregnancy. A significant portion of the participating women (more than half) were in the age range of 20 to 29 years, with university education, providing responses with high accuracy.

The current study included confounders such as age and education in the analysis, as well as the number of living children, folic acid use, and its relationship with the mood

			Used of folic acid				Chi-Square
			Regular	Irregular	Not used	Total	
Age	<20	n	3	15	38	56	10.401
		%	0.6%	3.0%	7.6%	11.2%	
	20-29	n	12	72	183	267	
		%	2.4%	14.4%	36.6%	53.4%	
	30-39	n	5	31	91	127	
		%	1.0%	6.2%	18.2%	25.4%	
	40-49	n	1	22	26	49	
		%	0.2%	4.4%	5.2%	9.8%	
	>50	n	0	1	0	1	
		%	0.0%	0.2%	0.0%	0.2%	
	Total	n	21	141	338	500	
		%	4.2%	28.2%	67.6%	100.0%	
Education	Illiteracy	n	1	18	35	54	14.501
		%	0.2%	3.6%	7.0%	10.8%	
	Primary	n	0	17	52	69	
		%	0.0%	3.4%	10.4%	13.8%	
	Secondary	n	2	31	81	114	
		%	0.4%	6.2%	16.2%	22.8%	
	University	n	18	75	170	263	
		%	3.6%	15.0%	34.0%	52.6%	
	Total	n	21	141	338	500	
		%	4.2%	28.2%	67.6%	100.0%	
No. Of child	One	n	2	28	85	115	4.61
		%	0.4%	5.6%	17.0%	23.0%	
	Two	n	8	46	96	150	
		%	1.6%	9.2%	19.2%	30.0%	
	>two	n	11	67	157	235	
		%	2.2%	13.4%	31.4%	47.0%	
	Total	n	21	141	338	500	
		%	4.2%	28.2%	67.6%	100.0%	

TABLE 2: Relationship between Participants features vs folic acid used

		used of folic acid	anxiety
Used of folic acid	Pearson Correlation	1	-0.642**
	Sig. (2-tailed)		.000
	N	500	500
Anxiety	Pearson Correlation	-0.642**	1
	Sig. (2-tailed)	.000	
	N	500	500
**, Correlation is significant at the 0.01 level (2-tailed).			
		used of folic acid	depression
used of folic acid	Pearson Correlation	1	-0.130**
	Sig. (2-tailed)		.003
	N	500	500
depression	Pearson Correlation	-0.130**	1
	Sig. (2-tailed)	.003	
	N	500	500
**, Correlation is significant at the 0.01 level (2-tailed).			

TABLE 3: Correlation between anxiety and depression vs folic acid used

of pregnant women. The results demonstrated that women in the age range of 20 to 29 years were more likely to use folic acid supplementation for more than three months during pregnancy. Moreover, they had higher education levels and had more than two children ($p < 0.05$).

As shown in Table 3, there is an inverse correlation between folic acid concentration and mood, which aligns with findings from other studies. Previous research found an inverse relationship between depression symptoms and serum folate status, particularly in women [15]. In a cross-sectional study of Japanese adolescent women, folate intake was inversely correlated with depressive symptoms. However, there was no clear correlation between folic acid intake and mood alterations [16]. Our study's estimates of the prevalence of

severe anxiety (55.8%) and moderate-to-severe depression (43.0%) were higher than those from similar studies. The prevalence of comorbidity varied across different populations due to sociocultural factors, family structure, and educational background [17], [18].

VI. CONCLUSION

Comorbid disorders such as depression and anxiety pose significant public health challenges as they indicate a higher susceptibility to social factors impacting health outcomes. Access to social support systems is crucial for pregnant women to mitigate these risks. Consistent folic acid use emerged as a key predictor, and various characteristics provided insights into comorbidity patterns during different

Used Anxiety	Used of folic acid							
	regular		irregular		not used		Total	
	n	%	n	%	n	%	n	%
mild anxiety	11	2.2%	35	7.0%	8	1.6%	54	10.8%
moderate anxiety	0	0.0%	106	21.2%	51	10.2%	157	31.4%
severe anxiety	10	2.0%	0	0.0%	279	55.8%	289	57.8%
Total	21	4.2%	141	28.2%	338	67.6%	500	100.0%

TABLE 4: Relationship between anxiety and folic acid used

Used depression	Used Of Folic Acid							
	regular		irregular		not used		Total	
	n	%	n	%	n	%	n	%
mild depression	0	0.0%	8	1.6%	6	1.2%	14	2.8%
moderate depression	0	0.0%	73	16.6%	71	12.2%	144	28.8%
moderate severe depression	0	0.0%	0	0.0%	215	40.0%	215	43.0%
severe depression	21	4.2%	60	15.0%	46	9.2%	127	25.4%
Total	21	4.2%	141	33.20%	338	62.60%	500	100.0%

TABLE 5: Relationship between depression and folic acid used

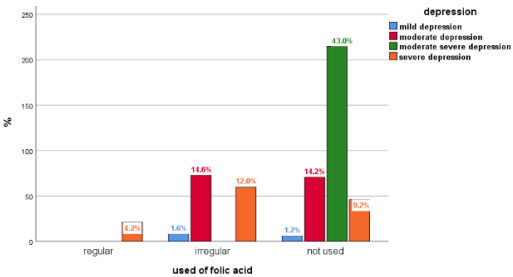


FIGURE 5: Relationship between depression and folic acid used

stages of pregnancy.

VII. RECOMMENDATION

Based on the findings of this study, it is recommended to encourage the introduction of folic acid to mitigate mood changes during the first trimester of pregnancy.

VIII. ACKNOWLEDGMENTS

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REFERENCES

[1] Reiner, R. C., Olsen, H. E., Ikeda, C. T., Echko, M. M., Ballestreros, K. E., Manguerra, H., ... Murray, C. J. L. (2019). Diseases, injuries, and risk factors in child and adolescent health, 1990 to 2017: Findings from the Global Burden of Diseases, Injuries, and Risk Factors 2017 Study. *JAMA Pediatrics*, 173(6), e190337-e.

[2] Kieling, C., Baker-Henningham, H., Belfer, M., Conti, G., Ertem, I., Omigbodun, O., ... Rahman, A. (2011). Child and adolescent mental health worldwide: Evidence for action. *The Lancet*, 378(9801), 1515-1525.

[3] Maas, A. I., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., ... Schwab, J. M. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology*, 16(12), 987-1048.

[4] Perrotta, G. (2019). Anxiety disorders: Definitions, contexts, neural correlates and strategic therapy. *Journal of Neurology & Neuroscience*, 6(1), 042.

[5] Kenny, D. (2011). *The Psychology of Music Performance Anxiety*. Oxford University Press.

[6] Horwitz, A. V., & Wakefield, J. C. (2012). *All we have to fear: Psychiatry's Transformation of Natural Anxieties into Mental Disorders*. Oxford University Press.

[7] Allen, R., James, A., & Sankaran, S. (2021). Trends in termination of pregnancy for neural tube defects in England and Wales from 2007 to 2017: Observational prospective study. *Prenatal Diagnosis*, 41(13), 1624-1633.

[8] Kelliher, L., Hennessy, Á., McCarthy, F., & Kiely, M. E. (2022). Periconceptional and antenatal nutritional supplement use in Irish women: Data from the improved study. *Proceedings of the Nutrition Society*, 81(OCE1).

[9] Ballestin, S. S., Campos, M. I. G., Ballestin, J. B., & Bartolomé, M. J. L. (2021). Is supplementation with micronutrients still necessary during pregnancy? *A Review Nutrients*, 13(9), 3134.

[10] Maruvada, P., Stover, P. J., Mason, J. B., Bailey, R. L., Davis, C. D., Field, M. S., ... Stabler, S. P. (2020). Knowledge gaps in understanding the metabolic and clinical effects of excess folates/folic acid: A summary, and perspectives, from an NIH workshop. *The American Journal of Clinical Nutrition*, 112(5), 1390-1403.

[11] Timmermans, S., Jaddoe, V. W., Hofman, A., Steegers-Theunissen, R. P., & Steegers, E. A. (2009). Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: The Generation R Study. *British Journal of Nutrition*, 102(5), 777-785.

[12] Maqbool, M., Dar, M. A., Gani, I., Mir, S. A., Khan, M., & Bhat, A. U. (2019). Maternal health and nutrition in pregnancy: An insight. *World Journal of Pharmacy and Pharmaceutical Sciences*, 8(3), 450-459.

[13] Saeed, M., Naveed, M., BiBi, J., Ali Kamboh, A., Phil, L., & Chao, S. (2019). Potential nutraceutical and food additive properties and risks of coffee: A comprehensive overview. *Critical Reviews in Food Science and Nutrition*, 59(20), 3293-3319.

[14] Sawaya, H., Atoui, M., Hamadeh, A., Zeinoun, P., Nahas, Z. (2016). Adaptation and initial validation of the Patient Health Questionnaire - 9 (PHQ-9) and the Generalized Anxiety Disorder - 7 Questionnaire (GAD-7) in an Arabic speaking Lebanese psychiatric outpatient sample. *Psychiatry Research*, 239, 245-252.

[15] Beydoun, M. A., Shroff, M. R., Beydoun, H. A., & Zonderman, A. B. (2010). Serum folate, vitamin B-12 and homocysteine and their association with depressive symptoms among US adults. *Psychosomatic Medicine*, 72(9), 862.

[16] Murakami, K., Miyake, Y., Sasaki, S., Tanaka, K., & Arakawa, M. (2010). Dietary folate, riboflavin, vitamin B-6, and vitamin B-12 and depressive symptoms in early adolescence: The Ryukyus Child Health Study. *Psychosomatic Medicine*, 72(8), 763-768.

[17] González-Mesa, E., Kabukcuoglu, K., Blasco, M., Körükcü, O., Ibrahim, N., González-Cazorla, A., ... & Arribas, A. (2020). Comorbid anxiety and depression (CAD) at early stages of pregnancy: A multicultural cross-sectional study. *Journal of Affective Disorders*, 270, 85-89.

[18] Bayramova, T. E., & Kazimi, M. M. (2019). Use of immunosuppressive drugs in pregnant women after organ transplantation. *Azerbaijan Pharmaceutical and Pharmacotherapy Journal*, 19(1), 43-47.