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FREQUENCY OF NEURAL TUBE DEFECT(NTD) AND ASSOCIATED ANOMALIES IN WOMEN WITH PERINATAL FOLIC ACID SUPPLEMENTATION PRESENTING TO HAYATABAD MEDICAL COMPLEX, PESHAWAR

Original Research

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ABSTRACT

Background: Neural tube defects (NTDs) are among the most common and severe congenital anomalies, with spina bifida and anencephaly being the most prevalent. Despite global advancements in prevention through periconceptional folic acid supplementation, NTDs continue to occur, particularly in low-resource settings. In developing countries, limited health education, suboptimal prenatal care, and overlooked maternal comorbidities may contribute to the continued burden of NTDs, even among supplement users.

Objective: To determine the frequency of neural tube defects and associated anomalies in women who reported periconceptional folic acid supplementation and to assess the association of NTDs with maternal and demographic variables.

Methods: A cross-sectional study was conducted at the Department of Obstetrics and Gynecology, Hayatabad Medical Complex, Peshawar, over six months. A total of 385 women aged 15–49 years who reported using folic acid at least one month before conception through two months after were enrolled using non-probability consecutive sampling. Data on demographics, health status, and ultrasound-confirmed NTDs were collected and analyzed using SPSS version 22. Mean and standard deviation were calculated for continuous variables, while frequencies and percentages were reported for categorical variables. Associations were tested using Chi-square and Fisher's Exact tests with a significance level set at $p < 0.05$.

Results: The frequency of NTDs was 2.3% (9 out of 385). No statistically significant association was observed between NTDs and maternal age (p=0.081), BMI (p=0.302), gravidity (p=0.350), parity, education level (p=1.000), socioeconomic status (p=0.282), dietary pattern (p=1.000), or cousin marriage (p=1.000). A statistically significant association was found between maternal comorbidities—such as anemia, hypertension, and diabetes—and NTDs (p=0.031).

Conclusion: Folic acid supplementation remains essential in reducing the incidence of NTDs; however, it is not universally protective. Maternal comorbid conditions may significantly increase the risk of NTDs. Preventive efforts must include comprehensive maternal health screening and management, alongside continued promotion of folic acid use.

Keywords: Anemia, Diabetes Mellitus, Folic Acid, Hypertension, Neural Tube Defects, Prenatal Care, Risk Factors.

INTRODUCTION

Neural tube defects (NTDs) remain a major public health concern globally, despite advances in prenatal care and preventive strategies. These congenital anomalies, primarily encompassing spina bifida and anencephaly, originate from the failure of the neural tube to close during early embryogenesis, often before a woman even realizes she is pregnant. Folic acid, a synthetic form of folate, has been widely established as a critical preventive measure against NTDs when taken during the periconceptional period (1). Numerous public health initiatives, including supplementation programs and food fortification policies, have been implemented to address the burden of NTDs, leading to substantial reductions in prevalence across many regions (2). Nevertheless, the persistence of NTDs—both isolated and those with associated anomalies—even in populations receiving folic acid, indicates a more complex and multifactorial etiology. While there is no denying the pivotal role of folic acid in reducing the incidence of NTDs, the continued reporting of such anomalies raises questions about the effectiveness of current strategies and the potential ceiling effect of folic acid alone (3,4). For instance, the study highlighted a notable decline in case severity of NTDs post-fortification, with a 70% reduction in severity and a 23% decline in the prevalence of spina bifida (4). Similarly, research in Brazil by Rodriguez and colleagues demonstrated that national flour fortification prevented thousands of NTD-affected births and saved millions in healthcare costs over a decade, underscoring the economic and medical benefits of such interventions (5). However, such progress must be balanced against findings that indicate persistent rates of isolated NTDs despite sustained supplementation efforts. A study found that although the overall prevalence of NTDs declined following fortification, isolated cases still comprised 74% of total NTDs, suggesting a possible plateau in the efficacy of folic acid alone (6,7).

The multifactorial nature of NTDs necessitates exploration beyond folic acid deficiency. Emerging studies now focus on other biochemical and genetic contributors, including maternal serum levels of folate receptors (FOLR1), which have been found to be significantly lower in women carrying fetuses with NTDs compared to those with unaffected pregnancies, indicating a potential role for receptor-mediated mechanisms in pathogenesis (8,9). Moreover, awareness regarding folic acid supplementation remains suboptimal in several low-resource settings. A recent Ethiopian study reported that over half of reproductive-aged women were unaware of the importance of preconception folic acid use, highlighting a critical gap in public health education (10-12). In the context of developing countries, the issue becomes even more complex. Despite ongoing prescription practices and a growing number of antenatal programs, a significant proportion of women remain unaware of the role of folic acid in preventing NTDs. This not only results in missed opportunities for prevention but also reflects the broader systemic challenges such as limited access to health education, fragmented antenatal care, and injudicious use of supplements without proper counseling. Addressing these gaps requires multifaceted strategies, including large-scale awareness campaigns, mandatory flour fortification, and further research into other causative factors to inform targeted interventions. Given these persistent challenges and the rising interest in exploring the limitations and broader context of folic acid supplementation, this study aims to determine the frequency of neural tube defects and associated anomalies in women with periconceptional folic acid supplementation.

METHODS

This cross-sectional study was conducted in the Departments of Obstetrics and Gynecology at Hayatabad Medical Complex (HMC), Peshawar, over a duration of six months following the approval of the research synopsis. The study aimed to determine the frequency of neural tube defects (NTDs) and associated anomalies in women who had received periconceptional folic acid supplementation. Ethical clearance was obtained from the institutional review board and the Research and Ethics Committee of the College of Physicians and Surgeons Pakistan (REU CPSP, Karachi), and all participants provided informed written consent prior to enrollment. Participants included women of reproductive age (15–49 years) who had taken folic acid during the periconceptional period, defined as one month before conception to two months post-conception. Women with serious or debilitating medical conditions such as carcinomas, eclampsia, epilepsy, or thalassemia were excluded to minimize confounding clinical variables. Additionally, individuals outside the defined reproductive age range or those who had not taken folic acid in the defined periconceptional window were also excluded from the study (13,14). A non-probability consecutive sampling technique was employed to recruit participants from both outpatient departments and inpatient wards. The sample size was calculated using WHO sample size calculator software, assuming an anticipated population proportion of 50% due to the absence of previous local estimates. A 95% confidence level and a 5% margin of error were applied, resulting in a final calculated sample size of 385 participants. The use of a 50% anticipated prevalence, although a common default in the absence of prior data, may not precisely reflect the local epidemiology and should be interpreted with caution.

Data were collected through structured interviews and validated medical records. Participants were asked about their use of folic acid during the periconceptional period, and those with positive findings of NTDs or associated anomalies on antenatal ultrasound were further assessed. Ultrasound findings suggestive of NTDs or related anomalies were reconfirmed via follow-up imaging performed by experienced radiologists or reliable diagnostic sources. Women with a prior history of pregnancies affected by NTDs were also included to identify potential recurrence despite supplementation. Collected data were entered and analyzed using SPSS version 22.0. Quantitative variables, including age, body mass index (BMI), gravidity, and parity, were summarized as means and standard deviations. Categorical variables such as education level, presence of comorbidities (e.g., anemia, diabetes, hypertension), and the occurrence of neural tube defects were presented as frequencies and percentages. Stratification was performed to examine the frequency of NTDs across different age groups, gravidity/parity levels, BMI categories, educational backgrounds, and comorbidity statuses. The Chi-square test was applied for post-stratification analysis to assess statistical significance at a 5% level.

RESULTS

A total of 385 women were included in the study. The mean age of participants was 26.48 ± 5.29 years, and the mean body mass index (BMI) was 24.06 ± 1.53 kg/m². The average number of pregnancies was 3.19 ± 1.48, and the average number of births was 1.88 ± 1.31, indicating that most participants were multigravida. The frequency of neural tube defects (NTDs) among women who had taken periconceptional folic acid supplementation was found to be 2.3%, with 9 confirmed cases out of 385 participants. Among these women, 55.8% (n = 215) were in consanguineous marriages, while 44.2% (n = 170) were not. However, no statistically significant association was observed between cousin marriage and the occurrence of NTDs (p = 1.000). Regarding dietary patterns, 98.4% (n = 379) were omnivores, 1.0% (n = 4) were vegetarians, and 0.5% (n = 2) were carnivores. No significant association was found between dietary habits and NTDs (p = 1.000). In terms of educational status, 74.8% (n = 288) of the participants were illiterate, 6.0% (n = 23) had primary education, 10.1% (n = 39) had secondary education, and 9.1% (n = 35) were graduates. Education level did not show a statistically significant relationship with the presence of NTDs (p = 1.000). Socioeconomic stratification revealed that 67.3% (n = 259) of women belonged to a lower socioeconomic class, 28.6% (n = 110) to the middle class, and 4.2% (n = 16) to the high-income group. No significant difference was observed in NTD prevalence across socioeconomic strata (p = 0.282). A total of 14.8% (n = 57) participants reported having comorbid conditions such as anemia, hypertension or pregnancy-induced hypertension, and diabetes mellitus types 1 or 2 or gestational diabetes. A statistically significant association was observed between the presence of maternal comorbidities and the occurrence of NTDs (p = 0.031), indicating that poor maternal health may play a contributory role in fetal neural tube development. Fisher's Exact Test was used where assumptions for the chi-square test were not met, specifically when expected cell counts were below 5. The test found no statistically significant associations between NTDs and maternal age (p = 0.081), BMI (p = 0.302), diet (p = 1.000), socioeconomic status (p = 0.282), cousin marriage (p = 1.000), education level (p = 1.000), and gravidity (p = 0.350). Only the presence of comorbid conditions reached statistical significance in its association with NTD occurrence.

Table 1: Descriptive Statistics of Maternal Characteristics

	N	Mean	Std. Deviation
Age Of Mother	385	26.48	5.285
Body Mass Index	385	24.057	1.5333
Total Pregnancies	385	3.19	1.479
Total Births	385	1.88	1.312
Valid N (Listwise)	385		

Table 2: Frequency Distribution of Key Variables and Their Association with Neural Tube Defects

Variable	Category	Frequency	Percent (%)	Valid Percent (%)	Cumulative Percent (%)	P-value
Neural Tube Defects	Yes	9	2.3	2.3	2.3	
	No	376	97.7	97.7	100.0	
	Total	385	100.0	100.0		
Cousin Marriage	Yes	215	55.8	55.8	55.8	1.000
	No	170	44.2	44.2	100.0	
	Total	385	100.0	100.0		
Type of Diet	Omnivores	379	98.4	98.4	98.4	1.000
	Vegetarians	4	1.0	1.0	99.5	
	Carnivores	2	0.5	0.5	100.0	
	Total	385	100.0	100.0		
Education Level	Illiterate	288	74.8	74.8	74.8	1.000
	Primary	23	6.0	6.0	80.8	
	Secondary	39	10.1	10.1	90.9	
	Graduate	35	9.1	9.1	100.0	
	Total	385	100.0	100.0		
Socioeconomic Status	Low	259	67.3	67.3	67.3	0.282
	Middle	110	28.6	28.6	95.8	
	High	16	4.2	4.2	100.0	
	Total	385	100.0	100.0		
Comorbidities (Anemia/HTN/DM)	Yes	57	14.8	14.8	14.8	0.031
	No	328	85.2	85.2	100.0	
	Total	385	100.0	100.0		

Table 3: Chi-Square and Fisher's Exact Test Results for Maternal and Demographic Variables Associated with Neural Tube Defects

Variable	Test Type	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Body Mass Index (BMI)	Pearson Chi-Square	0.862	1	0.353	0.608	0.302	
	Continuity Correction	0.171	1	0.679			
	Likelihood Ratio	0.721	1	0.396	0.608	0.302	
	Fisher's Exact Test				0.302	0.302	
	Linear-by-Linear Association	0.860	1	0.354	0.608	0.302	0.218
	Number of Valid Cases	385					
Maternal Age	Pearson Chi-Square	5.024	1	0.025	0.081	0.081	
	Continuity Correction	2.246	1	0.134			
	Likelihood Ratio	3.006	1	0.083	0.081	0.081	
	Fisher's Exact Test				0.081	0.081	
	Linear-by-Linear Association	5.011	1	0.025	0.081	0.081	0.071
	Number of Valid Cases	385					
Socioeconomic Status	Pearson Chi-Square	1.956	1	0.162	0.282	0.149	
	Continuity Correction	1.080	1	0.299			
	Likelihood Ratio	2.343	1	0.126	0.186	0.149	
	Fisher's Exact Test				0.282	0.149	

Variable	Test Type	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
	Linear-by-Linear Association	1.951	1	0.163	0.282	0.149	0.122
	Number of Valid Cases	385					
Cousin Marriage	Pearson Chi-Square	0.000	1	0.986	1.000	0.621	
	Continuity Correction	0.000	1	1.000			
	Likelihood Ratio	0.000	1	0.986	1.000	0.621	
	Fisher's Exact Test				1.000	0.621	
	Linear-by-Linear Association	0.000	1	0.986	1.000	0.621	0.263
	Number of Valid Cases	385					

Table 4: Chi-Square and Fisher's Exact Test Results for Associations with Neural Tube Defects

Variable	Test Type	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Maternal Education	Pearson Chi-Square	0.390	1	0.532	0.698	0.458	
	Continuity Correction	0.039	1	0.844			
	Likelihood Ratio	0.444	1	0.505	0.698	0.458	
	Fisher's Exact Test				1.000	0.458	
	Linear-by-Linear Association	0.389	1	0.533	0.698	0.458	0.315
	Number of Valid Cases	385					
Gravidity	Pearson Chi-Square	1.577	1	0.209	0.350	0.207	
	Continuity Correction	0.627	1	0.428			
	Likelihood Ratio	1.409	1	0.235	0.350	0.207	
	Fisher's Exact Test				0.350	0.207	
	Linear-by-Linear Association	1.570	1	0.210	0.350	0.207	0.158
	Number of Valid Cases	226					
Maternal Comorbidities	Pearson Chi-Square	6.418	1	0.011	0.031	0.031	
	Continuity Correction	4.238	1	0.040			
	Likelihood Ratio	4.671	1	0.031	0.031	0.031	
	Fisher's Exact Test				0.031	0.031	
	Linear-by-Linear Association	6.402	1	0.011	0.031	0.031	0.026
	Number of Valid Cases	385					

Table 5: Case Processing Summary for Variables Associated with Neural Tube Defects

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Neural Tube Defects * Age of Mother	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Body Mass Index	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Education Level	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Cousin Marriage	385	100.0%	0	0.0%	385	100.0%

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	Cases					
	Valid		**Missing**		**Total**	
	N	**Percent**	**N**	**Percent**	**N**	**Percent**
Neural Tube Defects * Type of Diet E.G Omnivores or Not	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Socioeconomic Status	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Any Comorbidity Like Anemia, HTN, DM	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Total Pregnancies	385	100.0%	0	0.0%	385	100.0%
Neural Tube Defects * Total Births	385	100.0%	0	0.0%	385	100.0%

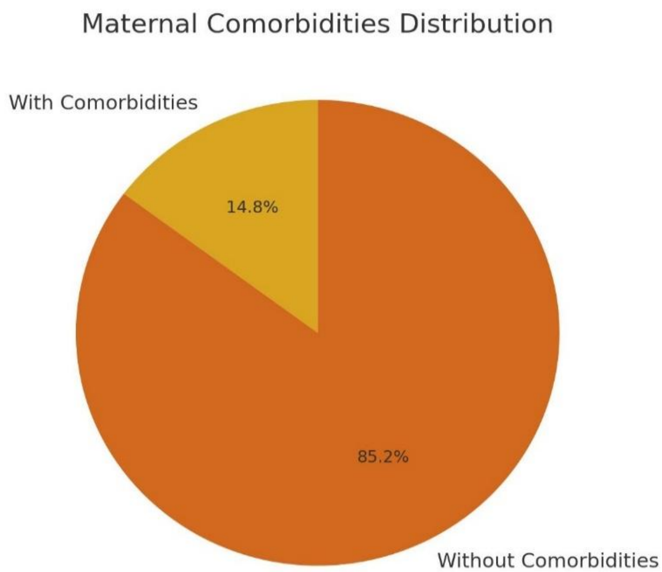

Figure 2 Maternal Comorbidities Distribution

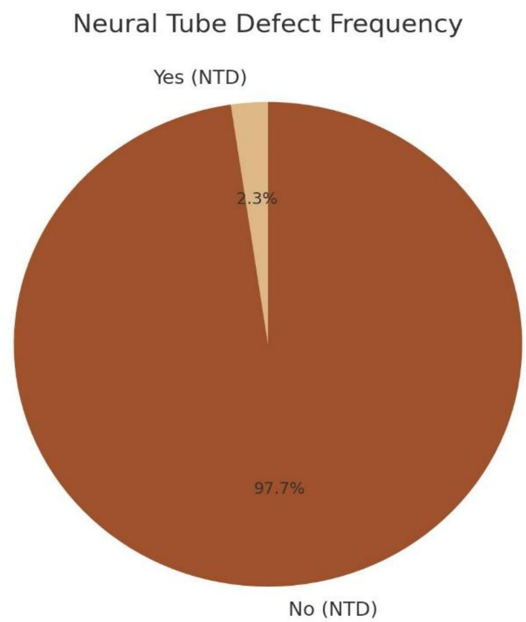

Figure 2 Neural Tube Defect Frequency

DISCUSSION

Building upon existing global evidence and addressing a notable gap in local data, the present study sought to determine the frequency of neural tube defects (NTDs) among women who reported taking folic acid during the periconceptional period. While international literature consistently supports the protective role of folic acid against NTDs, this study explored whether those protective trends persist in a local context, and whether maternal and demographic variables had any contributory associations. The overall frequency of NTDs among the participants was 2.3%, which, despite supplementation, aligns with findings from other regions that continue to report isolated and associated NTDs even after implementing folic acid fortification strategies (14,15). This study did not observe statistically significant associations between the presence of NTDs and maternal age, BMI, gravidity, parity, education, socioeconomic status, dietary habits, or cousin marriage ($p > 0.05$ for all). These findings contrast with previous research where maternal characteristics—especially poor awareness, low literacy, or poor dietary habits—were linked with increased risk of NTDs (16,17). However, the lack of significance in this study may be attributed to the sample size, limited power to detect weaker associations, or unmeasured confounding variables. A key strength of the study lies in its focus on a locally relevant population with detailed stratification, offering foundational data for future research and public health planning (18,19). Importantly, a statistically significant association was established between the presence of maternal comorbidities—including anemia, hypertension, and diabetes—and the occurrence of NTDs (p = 0.031). This finding aligns with a growing body of evidence that identifies chronic maternal health conditions as important risk factors in the etiology of congenital anomalies, including NTDs. Conditions such as pregestational diabetes and obesity are known teratogens that can interfere with embryonic development and disrupt gene expression involved in neural tube closure (20,21). Additionally, studies have linked elevated maternal blood glucose and sucrose levels to an increased risk of NTDs, irrespective of folic acid status (22,23). The present findings reinforce the notion that while folic acid plays a central preventive role, maternal metabolic health must also be optimized to effectively reduce the incidence of congenital anomalies.

Although no statistical significance was found for most sociodemographic variables, data trends indicated a higher frequency of NTDs among women from lower socioeconomic backgrounds and those with lower levels of education. This pattern, while not definitive, resonates with findings in resource-constrained settings where limited access to prenatal care, poor nutritional status, and lack of awareness contribute to the burden of birth defects. Additionally, the protective effect of folic acid may be mitigated by late initiation, suboptimal dosing, or non-compliance, factors which were not objectively measured in this study but remain plausible contributors to persistent NTD incidence. The limitations of this study are notable and must be acknowledged. As a single-centered study with a modest sample size, the generalizability of findings remains limited. Reliance on self-reported data introduces recall bias, particularly regarding the timing and duration of folic acid intake. The study did not assess compliance, dosage, or exact initiation timing of supplementation—critical variables in determining its effectiveness. Furthermore, several known or suspected contributors to NTDs, such as genetic predisposition, exposure to environmental toxins, medication use, and deficiencies in other micronutrients like vitamin B12 or zinc, were not included in the data collection or analysis. Despite these limitations, this study offers valuable insights into the ongoing prevalence of NTDs in a population where folic acid use is reportedly widespread. The observed association with maternal comorbidities underscores the importance of comprehensive prenatal care that goes beyond folic acid supplementation to include routine screening, diagnosis, and management of chronic conditions. These findings suggest a need for integrated maternal health strategies that combine supplementation programs with disease control and education initiatives. Future research should consider multicentric designs with larger, more diverse populations, and include objective verification of folic acid adherence, along with biochemical assessments of folate status (24,25). Incorporating genetic, nutritional, and environmental data would also help unravel the multifactorial nature of NTDs more precisely. Public health programs must continue to promote folic acid use, while simultaneously addressing maternal comorbidities through targeted interventions to effectively reduce the incidence of neural tube defects and improve pregnancy outcomes.

CONCLUSION

The study concluded that while the incidence of neural tube defects remains relatively low among women who use folic acid during the periconceptional period, these defects have not been entirely eliminated. Although factors such as maternal age, diet, education level, socioeconomic status, cousin marriage, gravidity, and parity appeared relevant, they did not show statistically significant associations. In contrast, maternal comorbidities emerged as a significant contributor to the occurrence of neural tube defects, highlighting the need for integrated prenatal care that not only promotes folic acid supplementation but also prioritizes early detection and management of maternal health conditions. These findings emphasize the importance of a comprehensive, multifactorial approach to preventing congenital anomalies in pregnancy.

AUTHOR CONTRIBUTION

Author	Contribution
Roman Bibi*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Ayesha khan	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Maimuna Aurangzeb	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Ghazala Shams	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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