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ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH FOLIC ACID SUPPLEMENTS RESISTANT SPINA BIFIDA IN ADDIS ABABA, ETHIOPIA: A CASE-CONTROL STUDY

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ABSTRACT

Background: *Spinabifida, one of the Neural tube defects (NTDs) is a preventable cause of morbidity and mortality worldwide and its burden is not well registered in low income countries. The aim of this study was to determine factors associated with folic acid supplements resistant spina bifida in Addis Ababa, Ethiopia.*

Methodology: *A case-control study was conducted in Zewditu Memorial Hospital, Addis Ababa, Ethiopia among mothers came for maternal and child health services. Both case and control participants were selected conveniently, consecutive participants were considered from their respective wards. Data were collected by trained nurses and midwives using structured template and analyzed by SPSS Version 21.0. Descriptive techniques and multiple binary logistic regression were employed. In all the statistical analysis, p-value < 0.05 was considered as statistically significant.*

Results: *A total of 225 mothers were approached for the study, and 219 (74 Cases Vs 145 Controls) of them were willing to participate. Of the mothers with a spina bifida birth outcomes, 52(70.3%) has gestational diabetes, 47 (63.5%) had poor adherence to folic acid supplementation. Mothers who are rural residents, and had gestational diabetes were more likely to have newborns with spina bifida (Adjusted Odds Ratio (AOR) =7.99 [95% Confidence Interval (CI): 3.99, 16.3]) and (AOR=5.01 [95% CI: 2.55, 10.04]) respectively.*

Conclusion: *Being diabetic during gestational age and rural residency were associated factors with folic acid supplements resistant spina bifida. Therefore, the government should give attention to rural and diabetic mothers to decrease the disease burden in the newborns.*

Key words: *Folic acid, Spina bifida, Pregnancy, Zewditu Memorial Hospital, Case-Control, Ethiopia.*

INTRODUCTION

Birth defects are one of the leading causes of infant mortality worldwide (1). Neural tube defects (NTDs) are a group of serious birth defects that affect the developing nervous system and include anencephaly, spina bifida, and encephalocele; which are among the most common birth defects worldwide. Spina bifida results from the failure of the vertebral arches to close over an open neural tube, exposing the spinal cord and nerves. Spina bifida is compatible with survival, although physical and occasional cognitive impairment occurs (2).

Globally, of the 2.76 million neonatal deaths in 2013, an estimated 276,000 babies died from congenital anomalies. NTDs are among the most common severe congenital defects (3). The global prevalence of open NTDs has varied from place to place. For instance, the prevalence in the United States is 1 case in every 2000 births, but in neighboring Mexico is significantly higher (4). A notable exception to this is the widespread decline in the prevalence of neural tube defects (anencephaly, spina bifida, and encephalocele) following the mandatory fortification of grain products with folic acid in several countries (5, 6).

Although folic acid supplement are safe and almost free of toxicity, a few studies have drawn attention to the possible adverse effects of using high doses throughout pregnancy (7) and at other stages of life (8). The current burden of folic acid supplements resistant spina bifida in Ethiopia is not registered well, and to the investigators knowledge and search there were no literatures found regarding the problem. Thus, there is a need to describe the current burden of folic acid supplements resistant spina bifida and identify its associated factors. Therefore, this study aims to determine factors associated with folic acid supplements resistant spina bifida in Addis Ababa, Ethiopia.

METHODOLOGY

Study area and period

The study was conducted in Zewditu Memorial Hospital, Addis Ababa, Ethiopia. The Hospital is affiliated to Addis Ababa City Administration Health Bureau. It is estimated to give clinical service to about 1.5 million catchment populations. Pediatric neurosurgery is available and children with spina bifida have a ward for admission.

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The data for this study were collected in the period August 25, 2017 to December 20, 2017.

Study population
All mothers visited Zewditu Memorial Hospital, pediatric wards during the data collection period and satisfy the study inclusion/exclusion criteria were considered a study population. The study population of mothers was classified in to controls and cases.

Cases: Mothers who took folic acid supplements during gestational age and had a child with spina bifida.

Controls: Mothers who took folic acid supplements during gestational age and had a child without spina bifida.

Inclusion criteria
All mothers who had delivery in the period 2014 to 2016 (to minimize the recall bias).

Exclusion criteria
Mother's who do not take folic acid supplements during gestational age.

Study design
A case-control study was conducted on mothers who took folic acid supplements during gestational age and came for maternal and child health services at the time of their appointment in Zewditu Memorial Hospital, during the data collection time.

Sample size determination and sampling
The sample size for this case control study was determined using the Fleiss 1981, formula with continuity correction. It was calculated using Epi Info™, version 7, whereas, the required information's, like proportions of controls with diabetic mellitus (DM) (P_0= 50%) and Odds ratio (OR= 2.5) were taken from previous studies (9, 10). Then, the final sample size with 95% confidence, 80% power, a 1:2 case to control ratio and 10% contingency was calculated to be 225 (75 cases and 150 controls). The final sample size was obtained by considering different exposures and DM was the exposure with the maximum sample size.

Once the sample size has been determined, the study participants were selected conveniently, consecutive participants were considered for the study. Cases were approached from pediatric neurosurgery ward and while controls were approached from other pediatric wards, when they came for maternal and child health services at the time of their appointment.

Data collection tool and procedure
The data were collected by trained midwifes and nurses using structured template prepared for this purpose, which was adopted from patient charts and by incorporating the study variables.

The data were collected from the patient chart and from the mothers when they came for maternal and child health services at the time of their appointment.

Study variables
Dependent variable: Folic acid supplements resistant spina bifida status (yes or no).

Independent variables: such as Socio-demographic factors (Mother's age, Monthly income, Mothers job, Marital status and Place of residence), Child factors (Child sex), and Maternal factors (Gestational body mass index (BMI), Contraceptives use, History of abortion, Gestational fever, Gestational DM, Drug use habit, Alcohol drinking habit, Smoking habit, Gestational stress, Folic acid supplements adherence and Gravida status).

Operational definition
a defect in the vertebral column with corresponding spinal cord and meninges protruding with or without cover by the overlying skin (11).

Folic acid supplements resistant spina bifida: the occurrence of spina bifida birth outcomes despite having folic acid supplementation history during gestational age (11).

Folic acid supplements adherence: as recorded on mothers chart.

Data quality management

Prior to the actual data collection, training was given to the data collectors. The investigators supervised the data collection and further checked the completeness and accuracy before leaving the actual data collection site. After collection, to minimize entry error and to increase data quality, entry was done on Epi Info™, version 7.

Data analysis

The collected data were analyzed by SPSS version 21. Descriptive statistics like mean, standard deviation, and frequency tables were used to describe study variables. A multiple binary logistic regression that takes in to account the binary nature of the outcome of interest and that can control confounding factors was used to identify factors associated with folic acid supplements resistant spina bifida. Adjusted odds ratios (AORs) with 95% confidence interval (CI) were used to quantify the magnitudes of association. And in all the statistical tests, variables with a p-value < .05 were considered statistically significant.

Ethical consideration

First, the proposal was approved by the Institutional Review Board (IRB) of Saint Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia. Then after, a support letter was written to Zewditu Memorial Hospital and permission was obtained. Finally, oral informed consent was taken from the study participants. Privacy and confidentiality were maintained, respectively by not exposing individual identifiers, and contain the data for research purpose only. Participants were told their participation is voluntary.

RESULTS

Socio-demographic characteristics of participants

A total of 225 mothers were approached for the study, and 219 (74 Cases Vs 145 Controls) of them were willing to take part in this study, which yielded a sample with non response rate of below the anticipated 10%.

The age of mothers ranges from 16 to 50 with a mean (±SD) age of 27.90 (±5.44 years). Above half of the mothers, 126 (57.5%) fall in the age group of 26-35 years, of them 39 (31%) were cases mothers. Among the urban residents 26 (17.6%) and 48(67.6%) of the rural residents, were mothers of cases. Most of the cases mother's 71 (95.6%) are married women, and above half of the cases 38 (54.1%) were female infants. Majority of the cases mother's 57(77%) had monthly income of less than 10,000 Ethiopian birr. Among the cases mother's, 45(60.8%) were housewife **(Table 1)**.

Tabe1: Sociodemographic characteristics of mothers with folic acid supplements resistant spina bifida birth outcomes Addis Ababa, Ethiopia, 2017 (n=219)

Variables	**Study Groups**	
	Cases, n (%)	**Controls, n (%)**
Mothers age (years)		
≤ 19	7(9.5)	3(2.1)
20-25	22(29.7)	41(28.3)
26-35	39(52.7)	87(60)
≥ 36	6(8.1)	14(9.7)
Monthly income (Birr)		
≥ 10,000	17(23)	40(27.6)
<10,000	57(77)	105(72.4)
Mothers job		
Housewife	45(60.8)	77(53.1)
Employed	19(25.7)	57(39.3)
Other	10(13.5)	11(7.6)
Residency		
Rural	48(64.9)	23(15.9)
Urban	26(35.1)	122(84.1)
Marital status		
Married	71(95.9)	128(88.3)
Unmarried	3(4.1)	17(11.7)
Sex (infant)		
Female	38(54.1)	71(49.1)
Male	36(48.6)	74(51)

Clinical profile of mothers

Twenty-eight (37.8%) cases mothers had normal (18.5-24.9) BMI at gestation compared to control mothers 61(42.1%). Compared to control mothers 39(26.9%); 52(70.3%) cases mothers had gestational DM. Relatively large proportion of control mothers (15.2%) had history of baby with spina bifida compared to cases mothers (2.7%) (Table 2).

Table 2: Clinical profiles of mothers with folic acid supplements resistant spina bifida birth outcomes Addis Ababa, Ethiopia, 2017 (n=219)

Variables	Study Groups	
	Cases, n (%)	Controls, n (%)
BMI (baseline)		
< 18.5	16(21.6)	23(15.9)
18.5-24.9	51(68.9)	98(67.6)
25-29.9	6(8.1)	21(14.5)
≥ 30	1(1.4)	3(2.1)
BMI (gestational)		
< 18.5	0(0)	2(1.4)
18.5-24.9	28(37.8)	61(42.1)
25-29.9	42(56.8)	60(41.4)
≥ 30	4(5.4)	22(15.2)
Contraceptives		
Yes	43(58.1)	96(66.2)
No	31(41.9)	49(33.8)
Abortion history		
Yes	17(23)	43(29.7)
No	57(77)	102(70.3)
Fever (gestational)		
Yes	29(39.2)	52(35.9)
No	45(60.8)	93(64.1)
Drug of abuse		
Yes	0(0)	10(6.9)
No	74(100)	135(93.1)
Alcohol drinking history		
Yes	0(0)	105(72.4)
No	74(100)	40(27.6)
Smoking		
Yes	0(0)	15(10.3)
No	74(100)	130(89.7)
Stress		
Yes	26(35.1)	63(43.4)
No	48(64.9)	82(56.6)
Parity		
Primigravidia	34(45.9)	54(37.2)
Multigravidia	40(54.1)	91(62.8)
Diabetic Status		
Yes	52(70.3)	39(26.9)
No	22(29.7)	106(73.1)
FA Adherence (as recorded in mothers chart)		
Poor	47(63.5)	85(58.6)
Good	27(36.5)	60(41.4)
Baby with Spina Bifida (history)		
Yes	2 (2.7%)	22 (15.2%)
No	72 (97.3%)	123 (84.8%)

Associated factors of folic acid supplements resistant spina bifida birth outcomes

In order to identify factors associated with folic acid supplements resistant spina bifida birth outcome a multiple binary logistic regression analysis was fitted by excluding variables with small a number of cell frequencies (< 10). Therefore, the variables mothers' age; monthly income; mother job; place of residence; child sex; contraceptives use; abortion; fever; diabetes mellitus; stress; adherence; and gravida were considered for the analysis.

Table 3: Factors associated with folic acid supplements resistant spina bifida birth outcomes Addis Ababa, Ethiopia, 2017 (n=219)

Variables	AOR (95%CI)	p-Value
Mothers age		.457
20-25	.92(.28, 2.98)	.888
26-35	1.56(.53, 4.57)	.422
≤ 19 or ≥ 36	1	.
Monthly income		
< 10,000	1.33 (.53, 3.32)	.546
≥ 10,000	1	
Mothers job		.402
Housewife	.43 (.13, 1.46)	.177
Employed	.49 (.14, 1.73)	.268
Other	1	
Residency		
Rural	7.99 (3.99, 16.03)	> .000*
Urban	1	
Child Sex		
Female	.92 (0.45, 1.89)	.828
Male	1	
Fever (gestational)		
Yes	1.12 (.52, 2.39)	.779
No	1	
Contraceptives use		
Yes	.96 (.44, 2.12)	.925
No	1	
Abortion history		
Yes	1.02 (.42, 2.49	.963
No	1	
Stress(gestational)		
Yes	.55 (.27, 1.13)	.105
No	1`	
Gravida		
Primigravidia	1.63 (.77, 3.44)	.202
Multigravidia	1	
Diabetic Status (Gestational)		
Yes	5.06 (2.55, 10.04)	> .000*
No	1	
Folic acid supplements adherence (as recorded in mothers chart)		
Poor	.96 (.45, 2.03)	.911
Good	1	

*p-value <0.05

The results of the multiple binary logistic regression analysis revealed that the variables place of residence, and gestational diabetes mellitus, were significantly associated with folic acid supplements resistant spina bifida birth outcome. In the multiple regression analyses, the odds/chance of getting baby with folic acid supplements resistant spina bifida birth outcome for women from rural areas was 7.99 times higher than those from urban areas. Mothers with gestational DM were 5.06 times more likely to have baby with folic acid supplements resistant spina bifida birth outcome than women who were not diabetic (Table 3).

DISCUSSION

The present work attempted to determine the clinical epidemiology and associated factors of folic acid supplements resistant spina bifida in Addis Ababa, Ethiopia. In this study, mothers with diabetes mellitus were more likely to have newborn with spina bifida. This finding is in line with those of previous studies (9, 10, 12, and 13). Further, in this study, mothers who were rural residents were more likely to develop spina bifida birth outcomes compared to urban residents. This finding is in line with a study done in China (14).

In this study, there was relatively large proportion of mothers with folic acid supplements resistant spina bifida in the age group 26-35 years unlike to the finding of a previous study (15). The proportion of folic acid supplements resistant spina bifida was higher in mothers with poor adherence towards folic acid supplementation and this finding is in line with that of a previous study (15), and another study has provided evidence that folic acid reduces the risk of spina bifida (16). Moreover, as to the finding of a previous study (17), less proportion of folate supplementation was found to be a risk factor for spina bifida.

Although, all the mothers had used folic acid supplementation during their gestational age with different adherence, those with good adherence of folic acid supplementation among control and cases were also with higher prevalence of folic acid supplements resistant spina bifida among each group. This finding is also in agreement with that of a previous study (18) that confirmed around 30-50 % of neural tube defects was not folate preventable, and other environmental factors must also be considered.

In this study, female children had most common resistant spina bifida among children with folic acid supplements. Being a female infant was thought to be a risk factor for development of neural tube defect including spina bifida as substantiated by a previous study (19).

Like control groups, most of the women with folic acid supplements resistant spina bifida cases were in gravidia II. This finding lacks statistical association with folic acid supplements resistant spina bifida in this study but in other previous study done in Egypt (17) it had shown a statistical significant association.

While revealing the undocumented/ unknown burden of folic acid supplements resistant spina bifida in the study set up, the study had some limitations; due to the fact that the mothers were busy in taking care of their child, it was not possible to spent much time to collect important variables like dietary patterns and identification of the total amount and time span of use (before/after conception) of folic acid supplements. In addition, though adherence was controlled via the regression, participants were recruited irrespective of their adherence to the folic acid supplement.

Conclusion and recommendation

Even though, good adherence to folic acid supplementation during pregnancy reduces the risk of folic acid supplements resistant spina bifida birth outcomes, still folic acid unpreventable spina bifida birth outcomes could occur. Place of residence and gestational diabetic status were factors associated with folic acid supplements resistant spina bifida. Due attention should be given to pregnant women residing in rural areas with gestational diabetes during pregnancy visit in health facilities.

Moreover, future studies that consider issues not addressed in the present study; like recruiting patients who have similar adherence status; studying dietary patterns and identification of the total amount and time span of use (before/after conception) of folic acid supplements are recommended to better understand the problem.

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Competing interests

The authors declare that this manuscript was approved by all authors in its current form and that no competing interest exists.

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