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Incidence and risk factors for neural tube defects in a Bosnian population

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ABSTRACT

Introduction: Neural tube defects (NTDs) are multifactorial congenital anomalies of the central nervous system that results from failed neural tube closure between the 3rd and 4th weeks of embryonic development. Numerous clinical and experimental studies indicate that supplementation with folic acid before and during early pregnancy reduces the development of these anomalies. The present study examined the incidence and risk factors for NTDs and evaluated the effects of folic acid supplementation.

Methods: This cross-sectional study included all children with NTDs who were hospitalized at the Pediatric Clinic, Clinical Centre University of Sarajevo during the period from January 01, 2008 to December 31, 2012. Data were collected retrospectively from the medical histories of hospitalized children. The study included children in pediatric clinics from four cantons (Sarajevo, Zenica–Doboj, Unsko–Sanski, and Central Bosnia) of the Federation of Bosnia and Herzegovina. The number of live births for the specified period in each of the four cantons was taken from a report by the Cantonal Ministry of Health.

Results: Among the 69,096 live births recorded during the study period, 39 children had verified NTDs, with an overall incidence of 0.56:1,000 (or 5.6:10,000) in all four cantons. The most common NTDs were myelomeningocele with hydrocephalus (22/39, 56.4%), followed by isolated myelomeningocele (9/39, 23.1%), spina bifida occulta (7/39, 17.9%), and occipitocele (1/39, 2.6%). A total of 33.3% (13/39) of mothers took folic acid, but only one began supplementation prior to pregnancy, while 67.7% (26/39) of mothers did not take folic acid during pregnancy. NTDs were found more frequently in primiparas (53.8%), women with low education (basic school, 64.1%), and unemployed women (82.1%).

Conclusion: It is important to make national recommendations for folic acid supplementation for women of reproductive age, but also change the public health policy that includes mandatory fortification of basic foods as this is the best measure for primary prevention of NTDs in the whole population regardless of employment and education status. Additional comprehensive studies are required to assess the incidence and risk factors throughout Bosnia and Herzegovina.

Keywords: Neural tube defects; incidence; folic acid; risk factors

INTRODUCTION

Neural tube defects (NTDs) are multifactorial congenital anomalies of the central nervous system that results from failed neural tube closure between the 3rd and 4th weeks of embryonic development. They consist of a spectrum of congenital malformations that include both cranial and spinal cord malformations. NTDs can be classified as "open" or "closed" types, based on the presence or absence, respectively, of exposed neural tissue. Severity depends on the level of the lesion, degree of damage to the exposed neural tissue, and the presence of Arnold–Chiari malformation. Closed defects (e.g., spina bifida occulta) can be completely asymptomatic and may be considered a variant of normal (1). Open NTDs are associated with severe, lifelong disability and high economic costs (2), and may also be the cause of miscarriage, intentional abortion, stillbirth, and infant mortality (3). More than 260,000 pregnancies worldwide are estimated to be affected by NTDs, and in newborns with NTD, 75% of cases leads to a lethal outcome before the age of 5 years (2).

The relationship between folic acid deficiency in women of reproductive age and the occurrence of NTD was first published in 1965 (4). Numerous randomized controlled studies have confirmed this hypothesis and demonstrated that folic acid supplementation reduces the occurrence of

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NTDs (4,5) if sufficient folic acid levels are achieved a few months before conception and during the 1st months of pregnancy, which is the period in which neural tube formation occurs (5).

Folic acid (Vitamin B_9) was isolated in 1941 from spinach leaves (lat. Folium). Other significant natural sources of folate include dark green leafy vegetables, yeast, legumes, mushrooms, meat, oranges, walnuts, and bananas. The body has only small reserves of folate that must be replenished daily (3). Folic acid is important for the synthesis of nucleic acids and the division, differentiation, and growth of embryonic cells. Pregnant women have higher daily requirements for folic acid (600 μg/day), which cannot be satisfied by usual food intake and requires supplementation.

Since 1993, national guidelines around the world have recommended that women of reproductive age take oral folic acid supplements for primary prevention at a dose of 400 μg/day, 3 months before conception and during the first 3 months of pregnancy. Women who have already had one pregnancy with NTDs should take 10 times the recommended dose (3). However, large numbers of unplanned pregnancies, insufficient knowledge about the importance of folic acid supplementation, and the cost of supplementation may explain the lack in expected results. Most women begin folic acid supplementation when they test positive for pregnancy, which is usually the time at which the neural tube is closed (6,7).

In 1998, the United States introduced a program of mandatory fortification of cereal products using 140 μg of folic acid per 100 g of cereals, and The Institute of Medicine's Food and Nutrition Board of the National Academy of Sciences recommended that all women who could become pregnant consume 400 μg of folic acid per day in addition to consuming food with folate from a varied diet to lower the chance of having a baby with an NTD (8). At present, around 85 countries, including the United States, have a program of mandatory enrichment of basic foodstuffs with folic acid, in contrast to Europe, where there are no mandatory fortification programs (7).

METHODS

Study Design

The present cross-sectional study included all children with NTDs who were hospitalized at the Pediatric Clinic, Clinical Centre University of Sarajevo during the period from January 01, 2008 to December 31, 2012. Data were collected retrospectively from the medical histories of hospitalized children.

We used a structured questionnaire to determine the type of NTD and as well as information about the mothers related to the number of births and taking folic acid. Data were collected from the medical histories of hospitalized children at the Department of Neonatology, Department of Neonatal Intensive Care, and Department of Neuropediatric of the Pediatric Clinic of the Clinical Centre University of Sarajevo. The survey included children in the pediatric clinics at four cantons of the Federation of Bosnia and Herzegovina (Sarajevo, Zenica–Doboj, Unsko–Sanski, and Central Bosnia). The number of live births for the specified period in the mentioned cantons was taken from the report of the Cantonal Ministry of Health.

Inclusion Criteria

The study included all newborns with verified NTD and data for maternal folic acid intake.

Statistical Analysis

Data were analyzed using Microsoft Excel (version 11, Microsoft Corporation, Redmond, WA, SAD) and compared with Chi-squared test. The results were elaborated and documented in detail and presented as absolute numbers, relative numbers, and statistical values with the use of statistical indicators. All *P*-values ≤0.05 were considered statistically significant.

RESULTS

The total number of live births in all four cantons during the study period (from January 2008 to December 2012) was 69.096, and 39 children had NTD, with an overall incidence of 0.56 per 1000. The highest incidence was in the Central Bosnia Canton with 1.07 per 1000 live births, followed by the Unsko–Sanski Canton with 0.60 per 1000, the Sarajevo Canton with 0.55 per 1000, and the Zenica–Doboj Canton where the incidence was statistically significantly lower at 0.25 per 1000 ($p < 0.0026$) (Table 1).

The gender distribution of children with NTD was uniform, with 54.4% boys and 45.6% girls. NTD was found more frequently in primiparas (53.8%), women with low education (basic school, 64.1%), and unemployed women (82.1%). There was no consanguinity between the parents, there was no maternal consumption of alcohol, and 17.9% (7/39) were smokers.

Folic acid supplementation was taken by 33.3% (13/39) of mothers during pregnancy, 12/13 women started taking folic acid after conception, and only one mother started supplementation before conception (Table 2). A total of 66.7% (26/39) of mothers did not take folic acid during pregnancy.

NTD types (Table 3) detected in the study included myelomeningocele (9/39; 23.1%), myelomeningocele associated with hydrocephalus (22/39; 56.4%), spina bifida occulta (7/39; 17.9%), and occipitocele (1/39; 2.6%). Among 39 children born with NTDs, 87.1% (34/39) survived and 12.9% (5/39) died.

DISCUSSION

The present study included 39 children with NTDs who were born during the period from January 2008 to December 2012 and hospitalized at the Pediatric Clinic, Clinical Center University of Sarajevo. In addition to children from the Sarajevo Canton, the study also included children from three cantons in Bosnia and Herzegovina who were transferred these to the pediatric clinic for diagnosis and treatment. The gender distribution in the present study was uniform (20 males and 19 females), which corresponds to the results of many studies (9,10); however, some studies have shown a higher frequency of congenital anomalies, including NTDs in females (6,10).

There was a decrease in the prevalence of NTDs, especially anencephaly and cervico–thoracic spina bifida in females, after the introduction of folic acid fortification, which led to a change in the sex distribution of infants with NTDs.

TABLE 1. Incidence of NTDs by canton

Canton	Number of live births	Number of live births with NTDs	Number of live births without NTDs	Incidence per 1,000 live births	$p<0.05$
Central Bosnia	12,131	13	12,118	1.07	N/A
Unskosanski	13,352	8	13,344	0.6	0.1893
Zenica–Doboj	19,986	5	19,981	0.25	0.0026*
Sarajevo	23,627	13	23,614	0.55	0.0833
Other cantons (no including Central Bosnia)	56,965	26	56,939	0.46	0.0096*
Total	69,096	39	69,057	0.56	N/A

Chi-square test was applied and the frequency of NTD by cantons was calculated. The lowest incidence was in the Zenica–Doboj Canton (0.25:1000; $P<0.0026$). Central Bosnia Canton had a significantly higher incidence (1.07:1000; P=N/A) and is compared with other cantons as well as the whole (not including Central Bosnia Canton) ($p<0.0096$)

TABLE 2. Characteristics of mothers

Characteristics	Cases	
	n	%
Education		
Basic	25	64.1
High school	14	35.9
University degree	0	0
Employment		
Yes	7	17.9
No	32	82.1
Smoking		
Yes	7	17.9
No	32	82.1
Alcohol consumption		
Yes	0	0
No	39	100
Consanguinity		
Yes	0	0
No	39	100
Parity		
First pregnancy	21	53.8
Second pregnancy	13	33.4
Multiple pregnancy	5	12.8
Miscarriage		
Yes	5	12.8
No	34	87.2
Comorbidity		
Yes	3	7.7
No	36	92.3
Received folic acid		
Yes	13	33.3
No	26	66.7
Timing of supplementation with folic acid		
Before conception	1	7.7
After conception	12	92.3

TABLE 3. Types of neural tube defect

Neural tube defect	n	%
Myelomeningocele	9	23.1
Spina bifida occulta	7	17.9
Myelomeningocele + hydrocephalus	22	56.4
Occipitocele	1	2.6
Total	39	100

Some mechanisms involved in this reduction in prevalence in females could be useful for identifying the pathogenesis of NTDs, especially those insensitive to folic acid (11).

The overall incidence of NTDs in our study was 39/69,096 (0.56 per 1,000), which is similar to the results of studies in Europe where the incidence of NTDs is 0.53 per 1,000 live births. This is higher than in the United States where the incidence is 0.39 per 1,000 (7).

The present study has some limitations. The incidence of NTDs was calculated on live births. If abortions are not included in the data but half of the identified cases are aborted, the data could show an artificial reduction in prevalence and incidence rates. However, it is unclear how much of an impact this could have on prevalence and incidence rates because abortion rates and advances in technology vary greatly by country (12).

Equality of incidence with European countries is likely a consequence of good health care of pregnant women and adequate nutrition of the entire population, particularly pregnant women who, according to our cultural habits, pay special attention to quality nutrition.

Analysis of the cantons in the present study showed a significant difference in the incidence of NTDs. The lowest incidence was in the Zenica–Doboj Canton (0.25:100; $p < 0.0026$), whereas the highest incidence was in the Central Bosnia Canton (1.07:1000; p = NA). The Central Bosnia Canton had significantly higher incidence compared to other cantons as well as the whole area (except SBK) ($p < 0.0096$) (Table 1).

Additional studies are required to determine the reason for the significant discrepancy in the incidence of NTDs in the cantons, especially since these are geographically small, close regions with ethnically identical populations.

Bosnia and Herzegovina are a developing country that lacks health programs. There are no official guidelines for taking folic acid in prenatal period, and pregnant women often start taking folic acid after their first visit to a gynecologist after they have found out they are pregnant. At this time the neural tube is usually closed, and folic acid intake during this period is ineffective in preventing NTDs.

The problem of unplanned pregnancies (which make up about 50% of all pregnancies) and delayed folic acid supplementation is also present in European countries where fortification of basic foodstuffs is not mandatory (13,14). Although voluntary folic acid fortification of some foods is available in much of Europe, European countries are reluctant to introduce mandatory fortification due to a fear of side effects. This mainly refers to the possibility of a link between folic acid and colon and bowel cancer, as well as an increase in blood folate levels that mask Vitamin B_{12} deficiency. In 1998, the US Food and Drug Administration issued guidelines for mandatory

fortification of cereal products with folic acid, and extended it to corn flour products in 2016, which led to a significant reduction in the incidence of NTDs (15).

In Bosnia and Herzegovina, there is currently no initiative for fortification of basic foodstuffs. Furthermore, there is not enough educated staff to make a prenatal diagnosis; therefore, prenatal diagnoses of NTDs are made late, and termination of pregnancy is not easy to implement, even when parents want it.

Inadequate nutrition without foods rich in folic acid is a significant risk factor for the development of NTDs (16,17). In the present study, none of the mothers consumed alcohol and none were blood-related to the father of the baby, which affects the development of NTDs because genetic factors, consanguinity, and alcohol consumption were detected as important risk factors for the development of NTDs (18). Analysis of the characteristics of mothers in the present study revealed that most mothers had low education levels (basic school, 64,1%) and were unemployed (82.1%), which may be risk factors for the development of NTD and should be investigated in future studies.

In the present study, meningomyelocele associated with hydrocephalus was the most common type of NTD (56.4%), which differs from the findings of a previous study (3) in which meningomyelocele was the most common congenital anomaly, although 10.7% were associated with hydrocephalus.

Meningomyelocele is the most common malformation, known as open spina bifida, and is a devastating congenital malformation of the central nervous system that is associated with significant morbidity. Open NTDs account for 80% of all NTDs (19).

Among 39 children born with NTDs, 87.1% (34/39) survived and 12.9% (5/39) died. The survival rate of these children is high worldwide, at around 92%. Most children survive with a severe lifelong disability that requires a long-term multidisciplinary approach and is associated with high economic costs and emotional difficulties for both the family and society. The lifetime direct cost of care per child born with spina bifida in the United States is estimated to be $768,000 (20).

CONCLUSION

Pregnant women often start taking folic acid after their first visit to a gynecologist when they find out they are pregnant. However, this is usually at a time when the neural tube is closed, and folic acid intake during this period is ineffective in preventing NTDs. Measures are required to achieve complete primary prevention of NTDs in Bosnia and Herzegovina. First, national guidelines for folic acid supplementation and fortification of basic foodstuffs would improve the folate status in women of reproductive age with low education levels, unemployed women, and many unplanned pregnancies with delayed supplementation. Second, education is also needed to emphasize the importance of these preventive strategies as well as national studies to analyze the frequency and risk factors for NTDs in Bosnia and Herzegovina and individually by canton.

Finally, the present study highlights the importance of NTDs, which are severe congenital anomalies that are accompanied by lifelong disability, high costs, and emotional difficulties for affected families and are preventable up to 70% cases.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

REFERENCES

1. Danzer E, Rintoul NE, Adzick MS. Pathophysiology of neural tube defects. In: Fetal and Neonatal Physiology. Elsevier; 2017. p. 1712-23.e4. https://doi.org/10.1016/b978-0-323-35214-7.00171-2.
2. Garrett GS, Bailey LB. A public health approach for preventing neural tube defects: Folic acid fortification and beyond. Ann N Y Acad Sci 2018;1414(1):47-58. https://doi.org/10.1111/nyas.13579.
3. Sher J, Frank JW, Doi L, Caestecker L. Failures in reproductive health policy: Overcoming the consequences and causes of inaction. J Public Health 2019;41(2):e209-15. https://doi.org/10.1093/pubmed/fdy131.
4. Hibbard BM, Hibbard ED, Jeffcoate TN. Folic acid and reproduction. Acta Obstet Gynecol Scand 1965;44(3):375-400. https://doi.org/10.3109/00016346509155874.
5. Wald NJ, Morris JK, Blakemore C. Public health failure in the prevention of neural tube defects: Time to abandon the tolerable upper intake level of folate. Public Health Rev 2018;39:2. https://doi.org/10.1186/s40985-018-0079-6.
6. Omer IM, Abdullah OM, Mohammed IN, Abbasher LA. Research: Prevalence of neural tube defects Khartoum, Sudan August 2014-July 2015. BMC Res Notes 2016;9(1):495. https://doi.org/10.1186/s13104-016-2298-6.
7. Turner MJ. Neural tube defects and folic acid food fortification in Europe. Am J Public Health 2018;108(5):601-2. https://doi.org/10.2105/ajph.2018.304389.
8. Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: A systematic analysis. Ann N Y Acad Sci 2018;1414(1):31-46. https://doi.org/10.1111/nyas.13548.
9. Liu J, Li Z, Ye R, Liu J, Ren A. Periconceptional folic acid supplementation and sex difference in prevention of neural tube defects and their subtypes in China: Results from a large prospective cohort study. Nutr J 2018;17(1):115. https://doi.org/10.1186/s12937-018-0421-3.
10. Larry JM, Paulozzi LJ. Sex difference in the prevalence of human birth defects, a population based study. Teratology 2001;64(5):237-51. https://doi.org/10.1002/tera.1070.
11. Poletta AF, Rittler M, Saleme C, Campaña H, Gili AJ, Pawluk SM, et al. Neural tube defects: Sex ratio changes after fortification with folic acid. PLoS One 2018;13(3):e0193127. https://doi.org/10.1371/journal.pone.0193127.
12. Frey L, Hauser WA. Epidemiology of neural tube defects. Epilepsia 2003;44(S3):4-13. https://doi.org/10.1046/j.1528-1157.44.s3.2.x.
13. Khoshnood B, Loane M, Walle H, Arriola L, Addor MC, Barisic I, et al. Long term trends in prevalence of neural tube defects in Europe: Population based study. BMJ 2015;351:h5949. https://doi.org/10.1136/bmj.h5949.
14. Botto LD, Lisi A, Robert-Gnansia E, Erickson JD, Vollset SE, Mastroiacovo P, et al. International retrospective cohort study of neural tube defects in relation to folic acid recommendations: Are the recommendations working? BMJ 2005;330(7491):571. https://doi.org/10.1136/bmj.38336.664352.82.
15. Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethan M, et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification-United States, 1995-2011. MMWR Morb Mortal Wkly Rep 2015;64(1):1-5.
16. Rehman L, Shiekh M, Afzal A, Rizvi R. Risk factors, presentation and outcome of meningomyelocele repair. Pak J Med Sci 2020;36(3):422-5. https://doi.org/10.12669/pjms.36.3.1237.
17. Flores A, Vellozzi C, Valencia D, Sniezek J. Global burden of neural tube defects, risk factors, and prevention. Indian J Community Health 2014;26(1):3-5.
18. Viljoen E. Harmful effects of smoking in pregnancy. S Afr Med J 2005;95(5):329-30.
19. Sahni M, Ohri A. Meningomyelocele. In: Stat Pearls. Treasure Island, FL: Stat Pearls Publishing; 2020.
20. Grosse SD, Berry RJ, Tilford JM, Kucik JE, Waitzman NJ. Retrospective assessment of the benefits of prevention: Folic acid fortification in the United States. Am J Prev Med 2016;50(5):S74-80. https://doi.org/10.1016/j.amepre.2015.10.012.