Original Article

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Investigation of the Change in the Incidence of Neural Tube Defects in the Eastern Black Sea Region of Turkey by Years and its Relationship with Folic Acid Use: A Case-control Study

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Abstract

Aim: This study aimed to determine the change in neural tube defects (NTD) incidence in Trabzon, a province of the Eastern Black Sea region, and evaluate the efficiency of folic acid use on NTD.

Methods: The present study was a retrospective case-control study. The case group of the study consisted of those diagnosed with fetal NTD in the intrauterine period between 2015 and 2020. The control group were selected by matching the ages in the case group with ± two standardized years. The total number of births in the province was obtained from the Turkish Statistical Institute data, and the NTD incidence was determined accordingly.

Results: Between the aforementioned years, the number of cases who had NTD-complicated pregnancies and were delivered in our clinic was 88. When the use of folic acid before and in the first trimester of pregnancy was compared, a statistically significant difference was determined between the groups ($p<0.001$). The use of folic acid during pregnancy was similar in both groups ($p=1$).

Conclusion: Neural tube defects is a preventable condition by using folic acid before and during the first trimester of pregnancy. Hence, the importance of using folic acid in family planning and prenatal counseling should not be forgotten.

Keywords: Black Sea, case-control study, folic acid, neural tube defects, pregnancy

Introduction

Neural tube defects (NTDs) occur congenitally between the embryological third and fourth weeks due to abnormal central nervous system development (1). NTD is rare and has a prevalence of 1 in 1,200 among live births in the United States and between 1 in 1,000 and 3-5 in 1,000 worldwide (2).

There are various factors in NTD etiology, such as drug exposure, geographical and ethnic differences, chromosomal abnormalities, single-gene disorders, folic acid deficiency, and family history of NTD (3). Pioneering studies on NTD by Smithells et al. (4) emphasized the importance of vitamin intake during pregnancy. Subsequently, a randomized, double-blind, placebo-controlled study by the MRC Vitamin Study Research Group in 1991 demonstrated that supplementation of 4 mg of folic acid daily resulted in a threefold reduction in the risk of NTD relapse (5). Today, NTD formation can be prevented at a significant rate of 15.5%-58% with maternal folic acid supplementation (6). The recommendation of folic acid use is the most critical part of preconception counseling regarding NTD prevention in family planning (7).

Although NTD incidence in Turkey varies between 3-5.8 per 1,000 according to the region, it is accepted as

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3 per 1,000 on average (8,9). In a guideline published by the Ministry of Health in Turkey in 2002, it was stated that all women of reproductive age should take daily folic acid supplementation during the preconception period and during the first trimester of pregnancy (10). The highest NTD frequency was observed in Northern and Eastern Anatolia in the previous studies and the lowest in Western Anatolia (11). The effect of Chernobyl on NTD has been discussed in prior studies examining the change in NTD incidence over the years in Trabzon province of the eastern Black Sea region (12).

At the time of these past studies performed in our clinic (12), folic acid supplementation had not been provided in Turkey. The present study aimed to determine the change in the incidence of NTD in Trabzon, a province of the Eastern Black Sea region, and to evaluate the efficiency of folic acid use on NTD.

Materials and Methods

Compliance with Ethical Standards

The ethical approval was obtained from the Karadeniz Technical University Faculty of Medicine Local Ethics Committee to perform the study (2020/266).

Study Design

The study was designed as a retrospective case-control study. The case group of the study consisted of those diagnosed with fetal NTD in the intrauterine period between 2015 and 2020 in the Department of Obstetrics and Gynecology of Karadeniz Technical University Hospital. The cases in the control group were selected by matching the ages in the case group with ± two standardized years. These controls were chosen from patients without any risk factors and did not require folic acid use due to any medical disease or condition or during pregnancy.

By matching the cases according to their ages, an equal number of cases were selected within the specified years, and the control group was formed.

The Gynecology and Obstetrics Clinic of our faculty hospital is a tertiary reference clinic in the Eastern Black Sea Region (provinces within this region include Rize, Artvin, Trabzon, Giresun, Ordu, Gumushane, and Bayburt) where fetal anomaly screenings are performed. The perinatology unit of this clinic is the primary perinatology center in the Eastern Black Sea Region. Like other similar studies, data for this study was collected from birth records and hospital automation systems. In this context, all NTD diagnoses (anencephaly, acrani, exencephaly, spina bifida, hydrocephalus, cephalocele, meningocele, meningomyelocele, encephalocele, iniencephaly, craniostosis, Arnold Chiari malformation) were reviewed from the hospital automation system to determine the incidence of NTD. The total number of births in the province was obtained from the Turkish Statistical Institute data, and NTD incidence was determined accordingly.

The incidence was calculated by dividing the number of births with NTD by the total number of births in the province in that year. Obviously, this will not give a direct NTD incidence because although our faculty hospital is the primary perinatology center in the province, the fact that the number of births with NTD in other hospitals in the province is unknown, making it an indirect incidence study. However, since most fetuses with anomalies were evaluated and delivered in our faculty, the total number of births in the province was considered the total number of births.

The cases in both the case and control groups were those who were born in our hospital regardless of their residence. As a result, possible sampling errors were attempted to be avoided.

After the cases were extracted from the records, they were called individually, and their pregnancies complicated by NTD were questioned. The use of folic acid before pregnancy, the use of folic acid in the first trimester of pregnancy, and whether they used folic acid-containing vitamins during pregnancy were asked and noted. Additionally, although they were available in the hospital records, their medical and drug use histories were also queried.

Statistical Analysis

The SPSS 21 program designed for Windows was used for the statistical analysis. All continuous variables were presented as mean and SD values, while categorical variables were expressed as percentages of the total group. A p-value of <0.05 was considered statistically significant, and all statistical tests were planned by comparing the two groups. An independent samples t-test compared categorical variables in the two groups. The chi-square test was used to compare cases and control groups, and the estimated risk was determined. Odds ratio analyses were performed, and the effect of folic acid use on NTD incidence was determined.

Results

Between the aforementioned years, the number of patients who had NTD-complicated pregnancies and were delivered in our clinic was 88. Considering the distribution of these cases by year, there were ten complicated pregnancy deliveries with NTD in 2015, while 12 deliveries occurred in 2020. The change in the incidence of NTD according to the number of births in Trabzon province by year was as presented in Figure 1. The highest incidence of NTD in the years indicated was in 2017, at 2 per 1,000 (Figure 1).

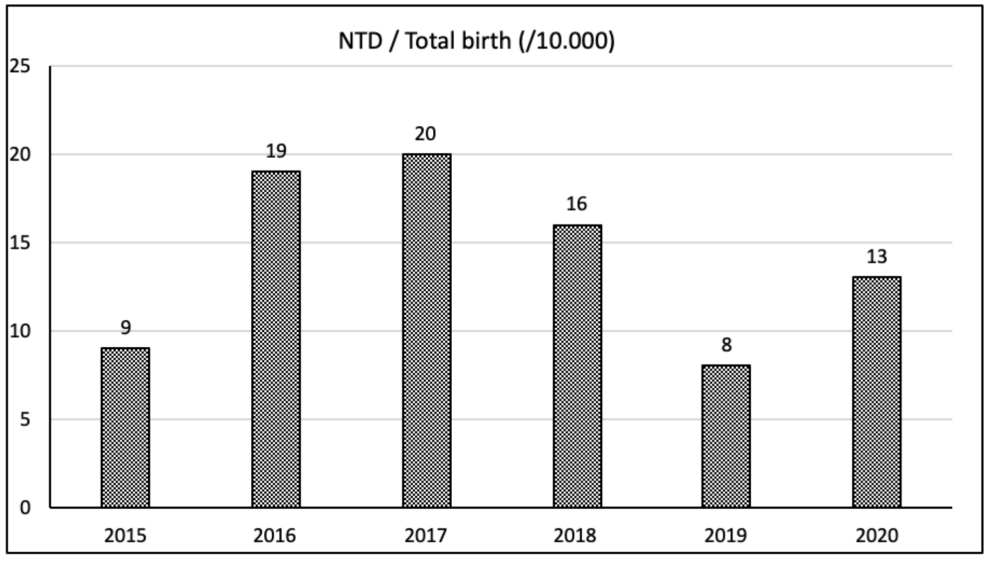

Figure 1. Change of NTD incidence by years
NTD: Neural tube defect

In the comparative analysis of the groups, there was no statistically significant difference in terms of age parameter (p=0.863) between the case and control groups regarding folic acid use. When the use of folic acid before and in the first trimester of pregnancy was compared, a statistically significant difference was determined between the groups (p<0.001). The use of folic acid during pregnancy was similar in both groups (Table 1).

The percentages of reducing the NTD risk by using folic acid before and in the first trimester of pregnancy were 91.2% and 91%, respectively (Table 2).

Discussion

According to the current study data, NTD incidence between 2015 and 2020 in Trabzon, where our clinic, the tertiary perinatology center of the Eastern Black Sea region of Turkey, is located, is between 0.8-2 per 1,000.

Table 1. Comparative analysis of the groups' mean age and folic acid use rates

	Case Group Pregnancy complicated with NTD (n=88)	Control Group Pregnancy uncomplicated with NTD (n=88)	p-value
Age	27.7±5.6	27.8±2.6	0.863'
Folic acid use before pregnancy	4 (4.5%)	31 (35.2%)	**0.000^**
Folic acid use in the first trimester of pregnancy	24 (27.3%)	64 (72.7%)	**0.000^**
Folic acid use during pregnancy (all trimesters)	18 (20.5%)	18 (20.5%)	1^

NTD: Neural tube defect
': Independent samples t-test, ^: The chi-square test

Table 2. The degree of effect of folic acid use on the NTD rate

	Case Group Pregnancy complicated with NTD (n=88)	Control Group Pregnancy uncomplicated with NTD (n=88)	p-value	OR	95% Confidence Interval	
					Lower	Upper
Folic acid use before pregnancy	4 (4.5%)	31 (35.2%)	**0.000'**	**0.088**	0.029	0.262
Folic acid use in the first trimester of pregnancy	24 (27.3%)	64 (72.7%)	**0.000'**	**0.090**	0.044	0.182

NTD: Neural tube defect
': The chi-square test and Odds ratio analysis

We observed that the use of folic acid before pregnancy prevented NTD by 91.2%, and its use in the first trimester by 91%. Consequently, the use of folic acid before and in the first trimester of pregnancy is found to be quite effective in preventing NTD. This effect is thought to be due to the contribution of folic acid to DNA formation between the third and fourth embryological weeks of neural tube development. The use of folic acid after the first trimester of pregnancy does not affect preventing NTD.

Neural tube defects occurs at a rate of 1-2 per 1,000 births in the world (13). The NTD rate is higher in countries with low or no folic acid use. In India, where the use of folic acid is uncommon, NTD incidence ranges from 6.5 to 8.2 per 1,000 births (stillbirths and live births) (14). In a Canadian study showing that the NTD rates decreased with the use of folic acid, the periods before and after the use of folic acid were compared. While NTD rates increased from 1986 to 1995, there was a decrease in NTD rates from 1995 to 1999 due to folic acid use (15). In Scotland, the fortification of cereal products with folic acid has been shown to reduce the incidence of NTD to 1.17 per 1,000 births (16). The average incidence of NTD in Trabzon between 2015 and 2020 was 1.44 per 1,000. This rate is similar to that in countries with folic acid use (13,16).

Folic acid use reduces NTDs, and all women of reproductive age should consume at least 400 µg folic acid per day to protect against NTDs (5). It is used at higher doses in high-risk groups (5,17). Low adherence to treatment, inability to receive preconceptional counseling due to unplanned pregnancies, low awareness of folic acid use, and stopping food supplementation due to unproven harm by European governments (18) stand out as the most critical problems in NTD prevention (19). Nevertheless, folic acid supplementation has been identified as the best approach to improving blood folate levels at a population level and has been mandated in several countries (10,20). Turkey also recommended using folic acid in the periconceptional period and the first trimester of pregnancy in 2002 to prevent NTD (10). In a study performed in Barcelona, a decrease in the prevalence of neonatal NTD was observed with primary prevention programs such as periconceptional folic acid supplementation (21). In our current study, we obtained results that support the previous studies. We have determined that the use of folic acid in the preconceptional period and the first trimester of pregnancy is quite efficient in preventing NTD. This study concluded that the risk of NTD decreased by 91.2% with the use of folic acid in the preconceptional period and by 91% with the use of folic acid in the first trimester of pregnancy. We revealed that the use of folic acid after the first trimester of pregnancy did not change the incidence of NTD ($p>0.05$). Several studies in the literature have reported that folic acid use throughout pregnancy has no effect on NTD and may affect homocysteine metabolism and the development of pre-eclampsia (22,23).

In our country, folic acid started to be used during pregnancy after the 2000s (10). When the studies before the 2000s were examined in a comparative analysis of the country's data and EUROCAT records (24), NTD rates were found to be high in Turkey (25). This is thought to be due to the later use of folic acid in the country compared to European countries. In Europe in the early 1980s, the incidence of NTD was much higher in the British Isles than in continental Europe (26), while the incidence of NTD in Turkey was very high even compared with rates in the British Isles in the 1980s (27). Mocan et al. (28) examined the population of Ankara, which was 3,235,637 in 1990, with the surrounding districts and villages. Before 1987, the incidence of NTD was 3.83 per 1,000 births (28). Some researchers have reported an NTD incidence of 1.5-2.6 per 1000 births in Turkey. The NTD rate in eastern Turkey has been reported as 4.5 (25). Himmetoglu et al. (29) reported that the overall incidence of congenital anomalies was 1.11%, and the incidence of NTD was 0.27% in their study population. Tunçbilek et al. (11) observed that 66 out of a total of 21,907 live births and stillbirths had NTDs. The incidence rate of NTDs was 30.1 per 10,000 births.

There are also studies after the 2000s when folic acid started to be used in our country. In 2000, the incidence of NTD was found to be 1.5 per 1,000 births in a study conducted by Mandiracioğlu et al. (30) in Izmir, western Turkey. Again, in a study performed in Afyonkarahisar, located in the west of the country, the incidence of NTD was 3.59 in 1,000 total pregnancies in 2004 (9). In a study conducted in Van province in eastern Turkey (31), the NTD rate was found to be 26 per 1,000 births between 2012 and 2015, and 13 per 1,000 births in another study between 2016 and 2018 (32). The authors considered that the slightly higher NTD rates than the actual rates were due to the low socioeconomic level and because the patients only applied to the hospital for delivery or in the late stages of pregnancy (31,32). In this study, the incidence of NTD in northeast Turkey has varied between 0.8 and 2 per 1,000 in the last five years. This rate is similar to the years after starting to use folic acid in Turkey and is lower than before the 2000s. The NTD rate in the northeast is similar to that in the west and has lower rates than in the east. We think that factors such as socioeconomic level, awareness of folic acid use, and regular follow-up of pregnancy may have caused this difference. We would like to emphasize once again how vital the use of folic acid is in preventing NTD.

Folic acid deficiency causes hypomethylation of DNA, insufficient DNA repair, and increased chromosomal breakage (3). One study revealed that folic acid deficiency increases spontaneous chromosome damage and interacts synergistically with ionizing radiation (33). Radiation causes congenital disabilities due to the ability of radioisotopes to bind to fetal cells, tissues, and DNA (34). The risk of radiation-induced anencephaly is increased in rat zygotes (34,35). Four radioactive fallouts have occurred to date: Hiroshima and Nagasaki (1945); Marshall Islands (1952), Chernobyl (1986), and Fukushima (2011). Many results, including researchers from our country, have been reported about the NTD formation of radioactive fallout after the Chernobyl disaster (12,14,28,36,37). However, the EUROCAT working group in Europe did not confirm the relationship between NTD and radiation (38). There are publications stating that NTD rates have increased due to the effect of radiation on the coast of Turkey facing the Black Sea (Bursa and Trabzon provinces) (12,37). By 1993, these high NTD rates in Turkey were attributed to interpretation errors and small hospital data sets (39). However, after the 2011 Fukushima disaster, the incidence of anencephaly and spina bifida in the western states of the USA increased by 13% compared to the pre-disaster period (40,41). In this context, the fact that two studies on the subject (12,37) were performed in the same hospital in the province of Trabzon, where our study was also conducted, fills a crucial gap in the literature with our current study. In the first study using Mocan et al. (37) in 1990, they stated that the continuing high incidence of NTD and anencephaly in 1988 and 1989 compared to previous years was probably due to the consumption of radioactive foods, especially tea, by the local people in this region. Again, in the second article published by the same team in 1992 (12), they continued the previous study from 1989 to the end of 1999 and stated the incidence of NTD as 6.16 per 1,000 births. They stated that the higher NTD rate might be because the records kept in the period from the previous study to this day were recorded more carefully (12).

In our current study, the mean NTD incidence (between 2015 and 2020) was 1.44 per 1,000 births, while the mean NTD incidence in the pre-Chernobyl period (between 1981 and 1986) was reported as 2.12 per 1,000 births, and 4.98 per 1,000 births in the post-Chernobyl period (between 1987-1990) (12,37). Considering the average NTD rate of 3.08 per 1,000 births between 1981 and 1990, this rate has dropped to the range of 0.8-2 after folic acid use. We can consider that folic acid reduces NTD rates once again. With these three NTD incidence studies performed in the same province between the 1980s and the 2010s, it is concluded that radiation does not have a long-term effect on creating NTD. The efficiency of folic acid use in this cannot be ignored. This brings to mind, "Is it possible that the reason why the long-term effects of Chernobyl do not continue is the use of folic acid?" which begs the question.

Study Limitations

Although our hospital is the reference center of the region regarding fetal anomalies, the fact that infants with NTD may have been delivered in other hospitals in the province or at home is unknown, and therefore a clear incidence cannot be given, and the retrospective design of the study can be considered a limitation of the study. The fact that it revealed the change in NTD incidence in the region after many years and the effect of folic acid on NTD incidence in our region, which is thought to have long-term effects of radiation, are also the study's strengths.

Conclusion

Neural tube defects is a preventable condition with the use of folic acid before and during the first trimester of pregnancy. Accordingly, the importance of using folic acid in family planning and prepregnancy counseling should not be forgotten. The NTD incidence in Trabzon, the reference center of the Eastern Black Sea Region, is similar to Turkey and world data. The effect of Chernobyl-related radiation on the incidence of NTD in the long term cannot be clearly demonstrated due to the use of folic acid, but it is concluded that the use of folic acid is also protective against a possible long-term effect of radiation.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Karadeniz Technical University Faculty of Medicine Local Ethics Committee to perform the study (2020/266).

Informed Consent: The present study was a retrospective case-control study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: O.D., H.S., M.T., Design: O.D., M.T., Data Collection and/or Processing: O.D., H.S., M.O., Analysis and/or Interpretation: O.D., H.S., M.O., M.T., Literature Research: O.D., H.S., M.O., M.T., Writing: O.D., H.S., M.O., M.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Greene ND, Copp AJ. Neural tube defects. Annu Rev Neurosci 2014;37:221-42.

2. 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;1414:31-46.
3. Mutlu H, Kızgut B, Sözer ÇS, Ürker K, Açar O, Erol AS. Sacral spina bifida occulta rare occurrence in Byzantine Belentepe population in Muğla, Turkey: A possible case for adequate folic acid intake. Homo 2020;71:175-88.
4. Smithells RW, Sheppard S, Schorah CJ, et al. Possible prevention of neural-tube defects by periconceptional vitamin supplementation. Lancet 1980;1:339-40.
5. MRC V. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338:131-7.
6. Pakdemirli A, Toksöz F, Karadağ A, et al. Role of mesenchymal stem cell-derived soluble factors and folic acid in wound healing. Turkish J Med Sci 2019;49:914-21.
7. Toivonen KI, Lacroix E, Flynn M, et al. Folic acid supplementation during the preconception period: A systematic review and meta-analysis. Prev Med 2018;114:1-17.
8. Altaş M, Aras M, Altaş ZG, Aras Z, Serarslan Y, Yılmaz N. Retrospective analysis of Neural Tube Defect Patients. MKÜ Tıp Dergisi 2012;3:22-8.
9. Onrat S, Seyman H, Konuk M. Incidence of neural tube defects in Afyonkarahisar, Western Turkey. Genet Mol Res 2009;8:154-61.
10. Tunçbilek E, Temel E, Özalp İ, et al. Genetic diseases. Handbook for health personel. TC Ministry of Health General Directory of Health Project. TR Ministry of Health General Directorate of Mother and Child Health and Family Planning, Ankara; 2002.
11. Tunçbilek E, Boduroğlu K, Alikaşifoğlu M. Neural tube defects in Turkey: prevalence, distribution and risk factors. Turk J Pediatr 1999;41:299-305.
12. Mocan H, Bozkaya H, Ozbay G, Mocan MZ, Aydemir V. Neural tube defects in eastern Black Sea region in 1990. Paediatr Perinat Epidemiol 1992;6:465.
13. Mai CT, Cassell CH, Meyer RE, et al. Birth defects data from population-based birth defects surveillance programs in the United States, 2007 to 2011: highlighting orofacial clefts. Birth Defects Res A Clin Mol Teratol 2014;100:895-904.
14. Singaravelu A, Vasantharajan SR, Raveendra R, Nancy A. Evaluation of Plasma Levels of Folic Acid and Homocysteine in Babies Born With Various Types of Neural Tube Defects: A Single Center Study in South India. Journal of Clinical and Basic Research 2022;6:28-31.
15. Gucciardi E, Pietrusiak MA, Reynolds DL, Rouleau J. Incidence of neural tube defects in Ontario, 1986–1999. CMAJ 2002;167:237-40.
16. Haggarty P. UK introduces folic acid fortification of flour to prevent neural tube defects. Lancet 2021;398:1199-201.
17. Petersen JM, Parker SE, Benedum CM, Mitchell AA, Tinker SC, Werler MM. Periconceptional folic acid and risk for neural tube defects among higher risk pregnancies. Birth Defects Res 2019;111:1501-12.
18. Wald NJ, Oakley GP. Should folic acid fortification be mandatory? Yes. BMJ 2007;334:1252.
19. Coll O, Pisa S, Palacio M, Quintó L, Cararach V. Awareness of the use of folic acid to prevent neural tube defects in a Mediterranean area. Eur J Obstet Gynecol Reprod Biol 2004;115:173-7.
20. Hertrampf E, Cortes F. Folic acid fortification of wheat flour: Chile. Nutrition reviews. 2004;62(suppl_1):S44-S8.
21. Salvador J, Arigita M, Carreras E, Lladonosa A, Borrell A. Evolution of prenatal detection of neural tube defects in the pregnant population of the city of Barcelona from 1992 to 2006. Prenat Diagn 2011;31:1184-8.
22. McNulty B, McNulty H, Marshall B, et al. Impact of continuing folic acid after the first trimester of pregnancy: findings of a randomized trial of Folic Acid Supplementation in the Second and Third Trimesters. Am J Clin Nutr 2013;98:92-8.
23. Wen SW, Guo Y, Rodger M, et al. Folic acid supplementation in pregnancy and the risk of pre-eclampsia—a cohort study. PLoS One 2016;11:e0149818.
24. Eurocat Working Group. Fifteen years of surveillance of congenital anomalies in Europe, 1980–1994. 1997;7:181.
25. Güvenc H, Uslu MA, Güvenc M, Ozekici U, Kocabay K, Bektaş S. Changing trend of neural tube defects in eastern Turkey. J Epidemiol Community Health 1993;47:40-1.
26. Prevalence of neural tube defects in 16 regions of Europe, 1980-1983. The EUROCAT Working Group. Int J Epidemiol 1987;16:246-51.
27. Rankin J, Glinianaia S, Brown R, Renwick M. The changing prevalence of neural tube defects: a population-based study in the north of England, 1984-96. Northern Congenital Abnormality Survey Steering Group. Paediatr Perinat Epidemiol 2000;14:104-10.
28. Mocan H, Aydemir V, Bozkaya H, Mocan MZ, Ozbay G. Incidence of neural tube defects (NTD) in Ankara, Turkey, prior to and after the Chernobyl disaster. Paediatr Perinat Epidemiol 1992;6:111-4.
29. Himmetoglu O, Tiras MB, Gursoy R, Karabacak O, Sahin I, Onan A. The incidence of congenital malformations in a Turkish population. Int J Gynaecol Obstet 1996;55:117-21.
30. Mandiracioğlu A, Ulman I, Lüleci E, Ulman C. The incidence and risk factors of neural tube defects in Izmir, Turkey: a nested case-control study. Turk J Pediatr 2004;46:214-20.
31. Peker E, Demir N, Tuncer O, et al. The levels of vitamın B12, folate and homocysteine in mothers and their babies with neural tube defects. J Matern Fetal Neonatal Med 2016;29:2944-8.
32. Ayaz R, Asoglu MR. Neural tube defects in eastern Turkey; Is low folate status or vitamin B12 deficiency or both associated

with a high rate of NTDs? The Journal of Maternal-Fetal & Neonatal Medicine 2020;33:3835-40.

33. Beetstra S, Thomas P, Salisbury C, Turner J, Fenech M. Folic acid deficiency increases chromosomal instability, chromosome 21 aneuploidy and sensitivity to radiation-induced micronuclei. Mutat Res 2005;578:317-26.
34. Guleria R, Bhushan B, Guleria A, Bhushan A, Dulari P. Harmful effects of Ionizing radiation. IJRASET 2019;7:887-9.
35. Maddox J., Gelineau-van Waes J, Starr L, et al. Maternal fumonisin exposure and risk for neural tube defects: mechanisms in an in vivo mouse model. Birth Defects Res A Clin Mol Treatol 2005;73:487-97.
36. Kruslin B, Jukić S, Kos M, Simić G, Cviko A. Congenital anomalies of the central nervous system at autopsy in Croatia in the period before and after the Chernobyl accident. Acta Med Croatica 1998;52:103-7.
37. Mocan H, Bozkaya H, Mocan MZ, Furtun EM. Changing incidence of anencephaly in the eastern Black Sea region of Turkey and Chernobyl. Paediatr Perinat Epidemiol 1990;4:264-8.
38. Dolk H, Nichols R. Evaluation of the impact of Chernobyl on the prevalence of congenital anomalies in 16 regions of Europe. EUROCAT Working Group. Int J Epidemiol 1999;28:941-8.
39. Little J. The Chernobyl accident, congenital anomalies and other reproductive outcomes. Paediatric Perinat Epidemiol 1993;7:121-51.
40. Akar N. Radioactive fallout and neural tube defects. Egyptian Journal of Medical Human Genetics 2015;16:299-300.
41. Mangano J, Sherman JD. Changes in congenital anomaly incidence in West Coast and Pacific States (USA) after arrival of Fukushima fallout. Open Journal of Pediatrics 2015;5:76-89.