Incidence of open neural tube defects in Nova Scotia after folic acid fortification

Research

Recherche

Vidia L. Persad, Michiel C. Van den Hof, Johanne M. Dubé, Pamela Zimmer

From the Department of Obstetrics and Gynaecology, Dalhousie University, Halifax, NS

This article has been peer reviewed.

CMAJ 2002;167(3):241-5

ß See related articles pages 237 and 255

Abstract

Background: With the goal of preventing open neural tube defects (NTDs), recommendations for folic acid supplementation before conception were introduced in Canada in 1994, and by November 1998 Canadian grain products were being fortified with folic acid. We wished to determine whether the annual incidence of open NTDs in Nova Scotia, including those in stillbirths and terminated pregnancies, changed after the introduction of either folic acid supplementation or fortification.

Methods: For the 10-year period from Jan. 1, 1991, to Dec. 31, 2000, we retrospectively extracted the total number of births in Nova Scotia and the number of live births and stillbirths with open NTDs from the Nova Scotia Atlee Perinatal Database as well as the number of terminated pregnancies affected by NTDs from the Fetal Anomaly Database. We determined the total annual incidence of all open NTDs, and of the subgroups spina bifida and anencephaly, per 1000 births in the province during the periods before (1991–1994) and after (1995–1998) folic acid supplementation initiatives were begun but before folic acid fortification of grain products was implemented, and during the periods before (1991–1997) and after (1998–2000) fortification.

Results: In the period after supplementation initiatives were begun but before fortification was implemented, the incidence of open NTDs did not change significantly: the mean annual rate was 2.55 per 1000 births during 1991–1994 and 2.61 per 1000 births during 1995–1997 (relative risk [RR] 1.02, 95% confidence interval [CI] 0.77–1.35). After the fortification was implemented the incidence of open NTDs decreased by more than 50%: the mean annual rate was 2.58 per 1000 births during 1991–1997 and 1.17 per 1000 births during 1998–2000 (relative risk 0.46, 95% CI 0.32–0.66).

Interpretation: The recommendations for folic acid supplementation alone did not appear to succeed in reducing the incidence of open NTDs in Nova Scotia, whereas the fortification of grain products with folic acid did result in a significant reduction in the incidence.

Open neural tube defects (NTDs) occur in 1–2 births per 1000 births and are the most significant fetal anomalies leading to long-term morbidity.[1] The lifetime medical and financial costs of a patient with spina bifida are very high, and the effect on the family is incalculable.[1] Periconceptional folic acid supplementation has been shown to reduce the prevalence of open NTDs by at least 60%.[2] This reduction occurred both among mothers with previously affected pregnancies and among those who have no such risk factors.[2] In 1991 a multicentre, prospective, randomized trial of folic acid supplementation in high-risk patients showed that a daily dose of 4 mg of folic acid was associated with a 71% reduction in the recurrence of open NTDs.[3] In 1992 Czeizel and Dudas[4] reported a similar reduction in the prevalence of open NTDs among low-risk women taking 0.80 mg of folic acid in a daily multivitamin preparation.

On the basis of this research, it became apparent that women planning pregnancies should be advised to take additional folic acid for 2 months before conception and throughout the first trimester.[5] The amount would depend on risk factors for open NTDs. Although the importance of folic acid was highlighted in 1991, a recommendation for preconceptional supplementation in Nova Scotia was not issued until February 1993.[3,6] Because half of pregnancies are unplanned,[7] health authorities subsequently recommended that all women capable of becoming pregnant should take folic acid supplements.[5–9] In late 1993 the Society of Obstetricians and Gynaecologists of Canada recommended that all women of child-bearing age consider taking 0.4 mg of folic acid or an adequate dietary equivalent daily,[8] and in 1994 the Canadian Task Force on the Periodic Health Examination further emphasized the importance of folic acid supplementation.[9]

Despite the importance of folic acid, many women still did not follow or were unaware of supplementation recommendations to prevent open NTDs. Between 1993 and 1999, studies showed that less than 45% of pregnant women reported having taken folic acid before conception.[10–13] As a result, investigators studied the effects of folic acid fortification as a means of increasing the daily intake of this vitamin.[14,15] Depending on the level of fortification, this was found to be effective at increasing serum folate levels to those that would correspond to a reduction of 22%–41% in the incidence of open NTDs.[15] In March 1996 the US Food and Drug Administration ordered that fortification with folate (0.14 mg per 100 g of grain) of all enriched grain products be implemented no later than Jan. 1, 1998.[16] Health Canada endorsed a similar fortification plan (0.15 mg per 100 g of grain) to be completed by Nov. 1, 1998.[17,18] This degree of fortification was aimed at reducing the annual incidence of open NTDs by an estimated 22%.[15] A recent large study on the effect of folic acid fortification in the United States showed a reduction of 19% in NTDs.[19] The data were retrieved from birth certificates, which raises validity concerns and does not take into account the large proportion of NTDs that are prenatally diagnosed and result in therapeutic abortion.[19] Population-based studies that include all NTDs (in live births, stillbirths and terminated pregnancies) have not previously been published and are needed to validate folic acid fortification measures.

The objective of our study was to evaluate the annual incidence of all open NTDs, including those occurring in stillbirths and terminated pregnancies, in Nova Scotia over a 10-year period. We identified the periods before and after folic acid supplementation initiatives were begun and the periods before and after folic acid fortification was implemented in order to study the effect of public health measures on the incidence of all open NTDs and the subgroups spina bifida and anencephaly.

Methods

We used a population-based retrospective study design to study all live births, stillbirths and terminated pregnancies in which open NTDs had occurred in Nova Scotia from Jan. 1, 1991, to Dec. 31, 2000. The Nova Scotia Atlee Perinatal Database encodes information on all births in Nova Scotia, with data abstracted from hospital records by trained registry personnel. Data include neonatal outcome, antenatal, intrapartum and postpartum variables, and maternal medical, socioeconomic and geographic variables. Standardized provincial antenatal, intrapartum and postpartum clinical forms help to ensure the collection of consistent information. Validation studies are performed periodically as part of the registry's quality assurance process, and the results have shown the data to be reliable.[20]

Nova Scotia offers both antenatal ultrasonographic and maternal serum α-fetoprotein screening for prenatal diagnosis of NTDs. All terminations of pregnancies affected by fetal anomalies in this province are undertaken in a single tertiary care centre, and the information is encoded and entered in the Fetal Anomaly Database by a trained person who helped develop the database and manages it. The information on fetal anomalies includes data on antenatal findings, and the final diagnosis is determined through postmortem pathologic examination or gross examination of fetal remains. Combining the data from the Nova Scotia Atlee Perinatal Database and the Fetal Anomaly Database allows for accurate population-based studies on birth defects. Final data on all births with open NTDs were available from both databases to Dec. 31, 2000. Because both databases provide identical specific variables on NTDs, affected cases were further divided into the subgroups spina bifida and anencephaly, as determined by antenatal ultrasonographic diagnosis, postmortem examination and examination at delivery.

Incidence rates were calculated as the total number of open NTDs occurring in live births, stillbirths and terminated pregnancies in Nova Scotia over the study period. We considered 1991–1994 to be the period before folic acid supplementation initiatives were begun and 1995–1997 as the period when public health measures on folic acid supplementation were in place but fortification had not yet begun. In 1996 concerns about the success of public health initiatives for supplementation led to the directive that grain products be fortified with folic acid by 1998. Although fortification may have begun in 1996, it was not complete until mid-1997.[16–18] Therefore, we considered 1991–1997 as the period before folic acid fortification and 1998–2000 as the period after fortification.

Results

There was a progressive decline in the total number of births in Nova Scotia, from 11 933 in 1991 to 9549 in 2000 (20% decline). There was also a decline in the absolute numbers of open NTDs, from 30 in 1991 to 9 in 2000 (70% decline) (Table 1).

There was no change in the total annual incidence of open NTDs in the period after folic acid supplementation initiatives were begun but before fortification was implemented (1995–1998): the mean annual incidence was 2.55 per 1000 births during 1991–1994 and 2.61 per 1000 births during 1995–1997 (relative risk [RR] 1.02, 95% CI 0.77–1.35; $p = 0.87$) (Table 1). Similarly, the mean annual incidence of spina bifida did not change significantly (1.44 and 1.60 per 1000 births respectively) (RR 1.11, 95% CI 0.79–

1.60; $p = 0.64$) (Table 2). Although there was a slight decline in the mean incidence of anencephaly after supplementation (from 1.00 to 0.82 per 1000 births), this change did not reach statistical significance (RR 0.82, 95% CI 0.51–1.32; $p = 0.49$) (Table 3).

The total annual incidence of open NTDs fell by 54% after the implementation of folic acid fortification, from 2.58 per 1000 births on average during 1991–1997 to 1.17 per 1000 births during 1998–2000 (Table 1) (RR 0.46, 95% confidence interval [CI] 0.32–0.66; $p < 0.001$). In the subgroup of spina bifida, the mean annual incidence decreased from 1.51 per 1000 births before to 0.62 per 1000 births after fortification (Table 2) (RR 0.40, 95% CI 0.25–0.67; $p < 0.001$). Similarly, for anencephaly the mean annual incidence decreased from 0.93 to 0.38 per 1000 births after fortification (Table 3) (RR 0.41, 95% CI 0.22–0.77; $p = 0.004$).

Interpretation

Folate is a water-soluble vitamin B complex first isolated from the spinach leaf in 1941[21] and synthesized in 1946. In 1960 Nelson[22] reported on the effects of folate deficiency on the development of rat embryos. Four years later Hibbard[23] suggested a possible relation between fetal malformation and defective folate metabolism. This relation was investigated in greater detail and, in 1965, Hibbard and Smithells[24] proposed the link between a defect in folate metabolism and NTDs in humans. Further studies led to the conclusion that folic acid intake before conception was an inexpensive, safe and effective method of primary prevention of open NTDs.[3,4,25–30] Debate about the merits of folic acid supplementation versus fortification then occurred. Although those opposed to fortification are concerned about the theoretical risk of exposing the entire population to additional folic acid, proponents argue that public education measures on the importance of preconception folic acid supplements and improved nutrition have not succeeded. This failure is likely due to the cost of public health initiatives, the difficulty in influencing lifestyle choices such as diet and the high rate of unplanned pregnancies.[31]

Our data show that, in the years before fortification, public education on the importance of folic acid supplementation had no significant effect on the incidence of open NTDs (Table 2). Because folic acid supplements taken before conception are known to be effective in preventing open NTDs, the lack of change in incidence rates was presumably due to an inability to change women's behaviour in taking preconceptual supplements. A random survey of 167 pregnant Nova Scotian women in 2001 showed that less than 50% had taken folic acid supplements before conception; other studies have shown similarly poor compliance rates.[10–13,32]

Because of the number of unplanned pregnancies and the failure of the folic acid supplementation strategies on their own, fortification of food with folic acid was initiated.[33] Fortification of food with nutrients has historically been successful in preventing such conditions as goiter (iodine deficiency), rickets (vitamin D deficiency), beri beri (thiamine deficiency), pellagra (niacin deficiency) and anemia (iron deficiency).[31] With folic acid fortification, there was concern about the risk of masking the diagnosis of pernicious anemia and its neurological sequelae. This condition primarily affects elderly people, but even in this group less than 1% of people over age 60 would be affected.[31] After careful deliberation, the US Food and Drug Administration called for folic acid fortification, but at a level that normally would limit daily intake to less than 1 mg.[16] This compromise was to ensure safety and at the same time allow a benefit to pregnant women that would correspond to a reduction of 6%–31% in the incidence of open NTDs.[15]

The results of our population-based study suggest that the folic acid fortification strategy was successful. In Canada folic acid fortification of grain products was mandated to begin in November 1998 at levels similar to those in the United States; however, most flour and pasta products were fortified as early as 1997 to harmonize with the US regulations, which came into effect on Jan. 18, 1998.[16–18] With the understanding that most fortification was completed by mid-1997, we chose 1998 as the start of the post-fortification period. Fortification should have a relatively abrupt ef-

Table 1: Annual incidence of open neural tube defects* (NTDs) in Nova Scotia before folic acid supplementation (1991–1994), after supplementation but before folic acid fortification (1995–1997) and after fortification (1998–2000)

Year	No. of cases of open NTDs: In live births and stillbirths	In terminated pregnancies	Total	Total no. of births†	Incidence per 1000 births
Pre-supplementation					
1991	18	12	30	11 933	2.51
1992	17	13	30	12 076	2.48
1993	14	16	30	11 715	2.56
1994	12	18	30	11 340	2.64
Post-supplementation/ Pre-fortification					
1995	5	18	23	10 913	2.11
1996	13	25	38	10 739	3.54
1997	8	14	22	10 125	2.17
Post-fortification					
1998	7	7	14	9 785	1.43
1999	1	10	11	9 676	1.14
2000	1	8	9	9 549	0.94
Total	96	141	239	107 851	2.22

*Includes spina bifida, anencephaly and encephaloceles.
†Live births, stillbirths and pregnancies terminated because of fetal anomalies.

fect, both on serum folate levels and on the incidence of open NTDs. Two studies have shown increased serum folate levels after fortification.[34,35] Our results showed a highly significant drop in the total incidence of open NTDs, taking into account all affected pregnancies (live births, stillbirths and terminated pregnancies); this dramatic drop was observed for both spina bifida and anencephaly. The inclusion of terminated pregnancies is particularly important because more than 50% of all affected pregnancies in Nova Scotia now result in therapeutic abortion. A failure to include terminated pregnancies may underestimate the benefit of folic acid fortification.[19]

The greater than anticipated reduction in the prevalence of open NTDs in our study could have been due to the fact that women may be receiving more folic acid from fortification than was originally calculated or that the calculated response was underestimated.[36] Alternatively, a higher background prevalence of open NTDs in Nova Scotia may reflect a population that was more sensitive to the influence of a folic acid effect. The abrupt decline that started in 1998 has continued, presumably because of more complete folic acid exposure as prefortification products are depleted. There would also be some crossover effect, as pregnancies delivered in early 1998 would be less likely to have been influenced by fortified products during early gestation (mid-1997) than pregnancies delivered later. For these reasons, it is expected that the reduction in incidence of open NTDs may be greater than 54%. If this significant decline can be verified for other geographic areas, it may suggest that the current level of fortification is adequate and that the controversial call for higher-dose fortification should await further studies.[37,38] Although our study highlights the effect of folic acid fortification, it does not preclude the additional benefit of supplementation. Undoubtedly, clinicians and researchers would agree that folic acid supplements remain an important adjuvant to fortification and that public education measures should not be abandoned.

Our study has limitations related to the arbitrary definitions used for the supplementation and fortification periods. The beginning of the supplementation period is poorly defined, and thus we chose the pre- and post-supplementation years on the basis of when public health measures were initiated and guidelines from relevant health authorities were released. In addition, mapping a temporal relation between folic acid supplementation and fortification strategies and the incidence of open NTDs does not prove a cause–effect relation, although it is highly suggestive.

Our results help to validate the decision to have food fortified with folic acid and may encourage the implementation of fortification in countries that have not yet implemented such strategies. The prevention of birth defects is a challenging goal, but current fortification measures appear to have successfully resulted in a reduction of

Table 2: Annual incidence of spina bifida

Year	No. of spina bifida cases: In live births and stillbirths	In terminated pregnancies	Total	Total no. of births*	Incidence per 1000 births
Pre-supplementation					
1991	11	5	16	11 933	1.34
1992	12	6	18	12 076	1.49
1993	11	5	16	11 715	1.37
1994	10	8	18	11 340	1.59
Post-supplementation/ pre-fortification					
1995	2	12	14	10 913	1.28
1996	9	16	25	10 739	2.33
1997	6	6	12	10 125	1.19
Post-fortification					
1998	5	3	8	9 785	0.82
1999	1	4	5	9 676	0.52
2000	1	4	5	9 549	0.52
Total	68	69	137	107 851	1.27

*Live births, stillbirths and pregnancies terminated because of fetal anomalies.

Table 3: Annual incidence of anencephaly

Year	No. of cases of anencephaly: In live births and stillbirths	In terminated pregnancies	Total	Total no. of births*	Incidence per 1000 births
Pre-supplementation					
1991	7	6	13	11 933	1.09
1992	3	7	10	12 076	0.83
1993	2	11	13	11 715	1.11
1994	2	9	11	11 340	0.97
Post-supplementation/ pre-fortification					
1995	2	6	8	10 913	0.73
1996	2	8	10	10 739	0.93
1997	2	6	8	10 125	0.79
Post-fortification					
1998	1	4	5	9 785	0.51
1999	0	3	3	9 676	0.31
2000	0	3	3	9 549	0.31
Total	21	63	84	107 851	0.78

*Live births, stillbirths and pregnancies terminated because of fetal anomalies.

at least 54% in the incidence of open NTDs in Nova Scotia. The effect of fortification in areas where the prevalence of NTDs is lower requires further study, as does the safety and long-term effects of fortification.

Competing interests: None declared.

Contributors: All of the authors were involved in developing the idea for this study. Most of the data analysis was undertaken by Dr. Persad, with some assistance by Dr. Dubé. Drs. Persad and Van den Hof were the principal authors; all other coauthors contributed to the revising of the article. All authors take full responsibility for the manuscript and its conclusions.

Acknowledgement: We acknowledge the Nova Scotia Atlee Perinatal Database and the Fetal Anomaly Database for contributing relevant data for our study.

References

1. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural tube defects. *N Engl J Med* 1999;341(20):1509-19.
2. Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects [review]. *Cochrane Database Syst Rev* 2000;(2):CD001056.
3. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Vitamin Study. *Lancet* 1991;338:131-7.
4. Czeizel AE, Dudas I. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *N Engl J Med* 1992;327:1832-5.
5. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep* 1992;41(RR-14):1-7.
6. Recommendations concerning the use of folic acid for the prevention of neural tube defects. Nova Scotia Prenatal Diagnosis Group. *Nova Scotia Med J* 1993;72:18.
7. Forrest JD. Epidemiology of unintended pregnancies and contraceptive use. *Am J Obstet Gynecol* 1994;170:1485-9.
8. Society of Obstetricians and Gynaecologists of Canada Genetics Committee. Recommendations on the use of folic acid for the prevention of neural tube defects. *J Soc Obstet Gynaecol Can* 1993;March(Suppl):41-6.
9. Beaulieu MD, Beagan BL. Primary and secondary prevention of neural tube defects. In: Canadian Task Force on the Periodic Health Examination. *Canadian guide to clinical preventive health care*. Ottawa: Health Canada; 1994. p. 74-81.
10. Sharpe G, Young G. Most pregnant women do not take folic acid. *BMJ* 1995; 311:256.
11. Wild J, Sutcliffe M, Scorah CJ, Levere MI. Prevention of neural tube defects. *Lancet* 1997;350:30-1.
12. Hutty WJ, Wald NJ, Walter JC. Folic acid supplementation before pregnancy remains inadequate [letter]. *BMJ* 1999;319:1499.
13. Use of folic acid-containing supplements among women of childbearing age — United States, 1997. *MMWR Morb Mortal Wkly Rep* 1998;47(7):131-4.
14. Cuskelly GJ, McNully H, Scott JM. Effect of increasing dietary folate on red-cell folate: implications for prevention of neural tube defects. *Lancet* 1996;347:657-9.
15. Daly S, Mills JL, Molloy AM, Conley M, Lee YJ, Kirke PN, et al. Minimum effective dose of folic acid for food fortification to prevent neural-tube defects. *Lancet* 1997;350:1666-9.
16. US Food and Drug Administration. Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid. *Federal Register* 1996;61:8781-97.
17. Bureau of Nutritional Sciences, Food Directorate, Health Protection Branch. *The addition of vitamins and minerals to foods; proposed policy recommendations*. Ottawa: Health Canada; 1999. Available (pdf format): www.hc-sc.gc.ca/food-aliment/english/subjects/dietary_reference_intakes/review_of_hc_policies/e_full_report.pdf (accessed 2002 July 3).
18. Turner LA, McCourt C. Folic acid fortification: What does it mean for patients and physicians? *CMAJ* 1998;158(6):773-4.
19. Honein MA, Paulozzi LJ, Mathews TJ, Erikson JD, Wong LC. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. *JAMA* 2001;285:2981-6.
20. Pair M, Cyr M, Allen AE, Wen SW, Guyen G, MacDonald RC. *Validation study for a record linkage of births and infant deaths in Canada*. Ottawa: Statistics Canada; 1999. Cat no 84F0013X1E.
21. Mitchell HK, Snell EE, Williams RF. Folic acid I. Concentration from spinach. *J Am Chem Soc* 1944;66:267-8.
22. Nelson MM. Teratogenic effects of pteroylglutamic acid deficiencies in rats. In: Wolstenholme GEW, O'Connor CM, editors. *CIBA Foundation symposium on congenital malformations.* London: Churchill Publishers; 1960. p. 134-51.
23. Hibbard BM. The role of folic acid in pregnancy. *J Obstet Gynaecol Br Commonw* 1964;71:529-42.
24. Hibbard ED, Smithells RW. Folic acid metabolism and human embryopathy. *Lancet* 1965;1254.
25. Smithells RW, Sheppard S, Schorak CJ. Vitamin deficiencies and neural tube defects. *Arch Dis Child* 1976;51(12):944-50.
26. Smithells RW, Sheppard S, Schorah CJ, Seller MJ, Nevin NC, Harris R, et al. Possible prevention of neural tube defects by periconceptional vitamin supplementation. *Lancet* 1980;1:339-40.
27. Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural tube defects. *BMJ* 1981;282:1509-11.
28. Smithells RW, Sheppard S, Schorah CJ, Seller MJ, Nevin NC, Harris R, et al. Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Arch Dis Child* 1981;56(12):911-8.
29. Smithells RW, Nevin NC, Seller MJ, Sheppard S, Harris R, Read AP, et al. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983;1:1027-31.
30. Hall JG. Folic acid: the opportunity that still exists [editorial]. *CMAJ* 2000; 162(11):1571-2.
31. Periconceptional use of folic acid for reduction of the risk of neural tube defects. Drug and Therapy Hazardous Substances Committee, Canadian Paediatric Society. *Paediatr Child Health* 1997;2(2):152-4.
32. Dawson LE, Ba' Pham, Hunter AGW. Low rate of adequate folic acid supplementation in well-educated women of high socioeconomic status attending a genetics clinic. *CMAJ* 2001;164(8):1149-50.
33. Daly S, Scott JM. The prevention of neural tube defects. *Curr Opin Obstet Gynecol* 1998;10:85-9.
34. Jacques PF, Selhub J, Bostom AG, Wilson PWF, Roseberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentration. *N Engl J Med* 1999;340:1449-54.
35. Lawrence JM, Petitti DB, Watkins M, Umekubo MA. Trends in serum folate after food fortification. *Lancet* 1999;354:915-6.
36. Rader JI, Weaver CM, Angyal G. Total folate in enriched cereal-grain products in the United States following fortification. *Food Chem* 2000;70:275-89.
37. Brent RL, Oakley GP, Mattison DR. The unnecessary epidemic of folic acid-preventable spina bifida and anencephaly. *Pediatrics* 2000;106:825-27.
38. Mills JL. Fortification of foods with folic acid — How much is enough? *N Engl J Med* 2000;342:1442-5.

Correspondence to: *Dr. Michiel C. Van den Hof, Department of Obstetrics and Gynaecology, Dalhousie University, 5980 University Ave., Halifax NS B3H 4N1; fax 902 425-1125; michiel.vandenhof@iwk.nshealth.ca*