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Canadian Paediatric Society
Société canadienne de pédiatrie

Statement

Periconceptional Use of Folic Acid for Reduction of the Risk of Neural Tube Defects

Neural tube defects

Neural tube defects are congenital malformations produced during intrauterine life by failure of closure of the neural tube, which eventually forms the central nervous system. Failure of closure typically at the cranial end of the neural tube results in anencephaly, or at the caudal neuropore end, in spina bifida. Neural tube defects are one of the most common congenital malformations seen among live-born infants in Canada and represent, after cardiac malformations, the second most prevalent congenital malformation associated with mortality in the immediate perinatal period.[1-5] They appear to be most often due to multifactorial inheritance but also occur as part of monogenetic disorders or are related to drug therapy during pregnancy with agents such as valproic acid and carbamazepine.[1,2,6-11]

The most common neural tube defects diagnosed at birth are spina bifida and anencephaly.[3,6,12] Anencephaly is not compatible with long-term survival.[13] Spina bifida can be surgically corrected, but surgical repair of the lesion is not always associated with improvement in motor function.

In Canada, the incidence of neural tube defects is between 1 and 4 cases per 1000 live births, with the highest rates occurring in Atlantic Canada; rates decline as one proceeds from east to west.[6,8,14,15] There are certain groups, such as those of Welsh, Irish and Sikh descent, who are at markedly higher risk for neural tube defects than is the general population.[16,17] The recurrence rate for women who have had a pregnancy which resulted in an infant with a neural tube defect is 2% (20 cases per 1000 live births), although in high-risk populations the recurrence risk may be 4 to 5% (40 to 50 cases per 1000 live births).[15]

Children with spina bifida frequently have long-term problems that require management by a multidisciplinary team. The economic impact of neural tube defects is difficult to assess. It has been estimated that approximately 800 children a year are born in Canada with neural tube defects, half of whom will have spina bifida. The direct health care costs for the children with spina bifida would be $1.7 million per year. This does not reflect the lost economic potential related to spina bifida,[8,18,19] or the psychosocial costs of spina bifida on children and their families. Health care costs for children with anencephaly are additional.

In the case of structural congenital anomaly, the possibility of prenatal screening and termination of affected pregnancies is an option in strategies to reduce the burden of disease. In the case of neural tube defects, prenatal screening using a combination of maternal serum alpha fetoprotein and obstetrical ultrasound can detect between 85 and 90% of affected pregnancies, if performed between 15 and 20 weeks of gestation. Women who have had a previously affected pregnancy can be tested by amniocentesis for measurement of amniotic fluid alpha fetoprotein, which will detect the presence of neural tube defects in greater than 95% of cases and is associated with a 0.5 to 1% risk of fetal loss.[20]

While prenatal screening for neural tube defects in low-risk populations can be performed with reasonable accuracy and reliability, no treatment is available *in utero* for the correction of neural tube defects. The option of termination is unacceptable for some patients, including those in the populations at highest risk. Given the limitations of prenatal screening, primary prevention of neural tube defects is an issue of considerable importance.

Folic Acid Supplementation

Diet and environmental factors have been implicated in the etiology of neural tube defects for some time. Attention has been focused on the potential impact of supplementation with folic acid on the incidence of neural tube defects. Over the past 15 years, there have been a number of clinical trials investigating the hypothesis that the use of folic acid in the periconceptional period is associated with a reduction in the risk for neural tube defects.[21-30] There have been four trials studying the effect of folic acid supplementation during the periconceptional period on the recurrence risk for neural tube defects. All four studies have concluded that folic acid supplementation in the periconceptional period is associated with a decrease in the risk for recurrence of neural tube defects.[21-24]

There have been four case-control studies, a cohort study, and an interventional study addressing the question of whether folic acid supplementation in the periconceptional period is effective in primary prevention of neural tube defects.[25-30] One of the case-control studies did not demonstrate any protective effects associated with folic acid supplementation in the periconceptional period. The other three case-control studies, the cohort study, and the interventional study, which was a prospective placebo-controlled study of 4573 pregnancies in Hungary, demonstrated reductions in the risk for neural tube defects among the patients who received folic acid supplementation.

These studies have resulted in the publication of recommendations with respect to the use of folic acid by women planning pregnancy by relevant bodies in Canada, the United Kingdom, and the United States.[8,15,31-33] In summary, the recommendation to women of child-bearing age is to consume 0.4 to 0.8 mg of folic acid per day for the purpose of reducing the risk of having a pregnancy affected with a neural tube defect. For women who have had a previous child with a neural tube defect, the daily dose range for prevention of recurrence appears to be between 0.8 and 4.0 mg of folic acid, although the optimal dosage has yet to be found.[8,15,30-33]

Adherence to the recommendations would be expected to decrease, but not abolish, the problem of neural tube defects. Studies demonstrating an effect typically show a 60 to 70% reduction in risk.[21-30] It is likely that, even in the face of universal compliance to the recommendations, there would continue to be cases of neural tube defect, reflecting the heterogeneity of the etiology of neural tube defects and the complex processes involved in the embryonic formation of the central nervous system.

However, the recommendation that all women considering pregnancy take supplemental folic acid is impractical for a large portion of the population. Approximately half of pregnancies in North America are unplanned. Given that folic acid supplementation appears to exert its protective effects with respect to neural tube defects during the periconceptional period, this would require that all women who could possibly become pregnant take folic acid supplements on a regular basis. The advice that women eat folate-rich foods is equally problematic, as this is both difficult and expensive.

Folic Acid Fortification

The alternative to folic acid supplementation is folic acid fortification of a staple in the food supply. This approach has been used to prevent goiter (iodine in salt), caries (fluoride in water), and rickets (Vitamin D in milk). In the United Kingdom, it has been suggested that bread would be a useful item to fortify. In Canada, some of the high-risk groups for neural tube defects do not consume bread on a routine basis, suggesting that another item in the food chain might be a more suitable item for fortification. An obvious choice would be flour. In Canada, small amounts of folic acid are already added to flour. The cost of increasing the folic acid content of flour would not be expected to be significant.

Fortification should aim to produce a daily dietary folic acid intake of between 0.5 and 1 mg, based on the usual dietary practices of women of child-bearing age.

This raises the question of the safety of folic acid fortification. Folic acid appears to be safe when taken chronically in doses as high as 10 mg per day.[34] Chronic toxicity would not be anticipated in the doses of folic acid that would be expected to be used in food fortification. The safety issue raised by food fortification relates to pernicious anemia, which is a disease caused by vitamin B_{12} deficiency, manifested clinically by megaloblastic anemia and neuropathy.[35,36] This disorder is relatively common among older Canadians, occurring in approximately 1% of patients aged 60 and above.The neurological complications can develop in the absence of macrocytic anemia. High-dose folic acid therapy can mask the hematological signs of pernicious anemia, while neurological complications such as posterolateral spinal-cord degeneration can progress.

Although this is an obvious concern, masking of hematological signs of pernicious anemia does not occur at the doses of folate recommended for primary prevention of neural tube defects. There have been no case reports of pernicious anemia masked by folic acid in these doses. In a survey of 860 hematologists, Butterworth was unable to find any evidence that such cases occur.[34] It appears that this dose of folic acid will not mask hematological features of pernicious anemia.

The exact safety of food fortification with folate to achieve the dietary goals recommended for primary prevention of neural tube defects is not known. The issue of food fortification is both complex and controversial. A problem is that the target population (women of childbearing age) is not the largest consumer of food. To achieve folic acid intakes near the desired dose in the target population, adult males, who are the largest consumers of food, would have significant increases in their folic acid intake.

Recommendations

Specific recommendations with respect to a strategy for reduction of the incidence of neural tube defects are:

1. That a large-scale trial be conducted to assess the impact of fortification of flour with folic acid to provide an average daily intake for women of child bearing age of between 0.5 and 1 mg per day.
2. That the incidence of neural tube defects be closely monitored after the initiation of the large-scale trial.
3. That a program of surveillance to study the incidence of pernicious anemia and the safety of food fortification with folic acid be put into place as a part of this clinical trial.
4. That the efficacy and safety of the food fortification trial be formally reviewed at 18 months and three years after the initiation of the program.
5. In the case that the trial demonstrates the efficacy and safety of food fortification with folic acid, that folic acid fortification be adopted as a matter of public policy with appropriate provision for ongoing monitoring of the safety and efficacy of this policy.

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This statement was also reviewed by the **Adolescent Medicine Committee** and the **Nutrition Committee** as well as approved by the Board of Directors of the Canadian Paediatric Society.