Recommendations on the use of folic acid supplementation to prevent the recurrence of neural tube defects

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Objective: To prevent the recurrence of neural tube defects (NTDs) in families at increased risk of having offspring with NTDs with the use of periconceptional folic acid supplementation.
Options: Genetic counselling and prenatal diagnosis of NTDs.
Outcomes: NTDs cause stillbirth, neonatal death and severe disabilities. The cost for medical care and rehabilitation in the first 10 years of life of a child with spina bifida cystica was estimated to be $42 507 in 1987.
Evidence: The authors reviewed the medical literature, communicated with investigators from key studies, reviewed policy recommendations from other organizations and drew on their own expertise. A recent multicentre randomized controlled trial showed that among women at high risk of having a child with an NTD those who received 4 mg/d of folic acid had 72% fewer cases of NTD-affected offspring than nonsupplemented women. Two previous intervention studies also demonstrated that folic acid supplementation was effective in reducing the rate of NTD recurrence. Several retrospective studies support this conclusion.
Values: Recommendations are the consensus of the Clinical Teratology Committee of the Canadian College of Medical Geneticists (CCMG) and have been approved by the CCMG Board. The committee believes that primary prevention of NTDs is preferable to treatment or to prenatal detection and abortion.
Benefits, harms and costs: Folic acid supplementation should result in fewer NTDs among infants in Canada and ancillary savings in medical costs. The recommended dosage of folic acid is not known to be associated with adverse effects. Higher dosages of folic acid may make vitamin B_{12} deficiency difficult to diagnose and may alter seizure frequency in patients with epilepsy due to drug interactions with anticonvulsants.
Recommendations: A minimum dosage of folic acid of 0.8 mg/d, not to exceed 5.0 mg/d, is recommended along with a well-balanced, nutritious diet for all women who are at increased risk of having offspring with NTDs and who are planning a pregnancy or may become pregnant. Supplementation should begin before conception and continue for at least 10 to 12 weeks of pregnancy.
Validation: These guidelines are similar to those of the Society of Obstetricians and Gynae-

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cologists of Canada, the US Centers for Disease Control and Prevention and the Department of Health in Britain.
Sponsors: These guidelines were developed by the CCMG Clinical Teratology Committee and endorsed by the Board of the CCMG. No funding for the development of these guidelines was obtained from any other sources.

Objectif : Prévenir, à l'aide de l'administration d'un supplément d'acide folique préconceptionnel, la récurrence des anomalies du tube médullaire dans les familles à risque élevé d'avoir des descendants ayant une anomalie du tube médullaire.
Options : Conseils génétiques et diagnostic prénatal d'anomalie du tube médullaire.
Résultats : Les anomalies du tube médullaire entraînent la mortinatalité, la mortalité néonatale et des invalidités sévères. Le coût des soins médicaux et de la réadaptation, au cours des 10 premières années de vie d'un enfant atteint d'hidrorachis externe rétromédullaire, a été estimé à 42 507 $ en 1987.
Preuves : Les auteurs ont revu la littérature médicale, ont communiqué avec les enquêteurs d'études clés, ont analysé les recommandations de politique d'autres organismes et se sont fiés à leur propre compétence. Un essai comparatif randomisé et multicentrique a démontré que, parmi les femmes à risque élevé d'avoir un enfant ayant une anomalie du tube médullaire, il y a 72 % moins de cas d'anomalie du tube médullaire des nouveau-nés, chez celles ayant reçu 4 mg/d d'acide folique que chez celles n'ayant pas reçu de supplément. Deux études antérieures sur le terrain ont aussi démontré que l'administration de suppléments d'acide folique est efficace pour réduire le taux de récurrence d'anomalies du tube médullaire. Plusieurs études rétrospectives appuient cette conclusion.
Valeurs : Les recommandations sont un consensus du Comité de tératologie clinique du Collège canadien de généticiens médicaux (CCGM) et ont été approuvées par le Conseil du CCGM. Le Comité croit que la prévention en première ligne des anomalies du tube médullaire est préférable au traitement ou à la détection prénatale et à l'avortement.
Avantages, préjudices et coûts : L'administration de suppléments d'acide folique devrait avoir pour résultat une diminution des anomalies du tube médullaire chez les nouveau-nés au Canada et, accessoirement, une diminution des coûts médicaux. On ne connaît pas d'effet adverse associé à la dose recommandée d'acide folique. Des doses plus élevées d'acide folique peuvent rendre plus difficile le diagnostic d'une déficience en vitamine B_{12} et modifier la fréquence des attaques dues aux interactions médicamenteuses avec les anticonvulsivants chez les patientes atteintes d'épilepsie.
Recommandations : Une dose minimale de 0,8 mg/d d'acide folique, sans excéder 5,0 mg/d, est recommandée, conjointement avec un régime alimentaire bien équilibré et nutritif, pour toutes les femmes à risque élevé d'avoir des descendants ayant une anomalie du tube médullaire et qui ont l'intention de devenir enceintes ou pourraient devenir enceintes. L'administration d'un supplément devrait commencer avant la conception et se poursuivre pendant au moins 10 à 12 semaines de grossesse.
Validation : Ces lignes directrices sont similaires à celles de la Société des obstétriciens et gynécologues du Canada, des Centers for Disease Control and Prevention des États-Unis et du ministère de la Santé de Grande-Bretagne.
Commanditaires : Ces lignes directrices ont été mises au point par le Comité de tératologie clinique du CCGM et sanctionnées par le Conseil du CCGM. Aucune subvention destinée à leur mise au point n'a été obtenue à d'autres sources.

Neural tube defects (NTDs), including spina bifida, anencephaly and encephaloceles, occur in about 1.6 per 1000 births in British Columbia,[1] Alberta[2] and Ontario[3] and in up to 4.0 per 1000 births in Newfoundland[4] and Quebec.[5] The causes of NTDs are most commonly multifactorial, with a recurrence risk for a couple who have had a previous fetus or infant with an NTD of 2.1% in British Columbia,[1,6] 2.2% in Alberta,[2] 2.4% in Ontario,[3] 4.5% in Quebec[7] and 5% in Newfoundland.[4] Certain groups in Canada are at higher risk than others of NTD occurrence and recurrence.[8] Families in which NTDs are caused by monogenic disorders, chromosomal abnormalities or teratogenic exposures have specific independent recurrence risks.[9–11]

Genetic counselling is available for prospective parents at increased risk of having a child with an NTD. This includes men and women who have had a child with an NTD, who are themselves affected with an NTD, who have a close relative with an NTD or who have a medical condition or are on medication that places their children at increased risk. Before folic acid supplementation, the only option available for high-risk couples who wished to reduce the chance of having children with NTDs was prenatal detection followed by abortion of an affected fetus.

There are important social and economic conse-

quences associated with NTDs. These severe congenital anomalies result in stillbirth, neonatal death and serious disabilities. In 1987 in Canada the estimated cost for hospital and rehabilitation services in the first 10 years of life for a child with spina bifida cystica was $42 507.[12] The cost is even higher when continuing health problems, special education needs, modifications of home facilities and career options are considered.

Methods

The Clinical Teratology Committee of the Canadian College of Medical Geneticists (CCMG) formulated guidelines to reduce the frequency of recurrence of neural tube defects (NTDs) in families that have children affected by NTDs. These recommendations are the result of a review of the medical literature; personal communication by members of the committee with investigators from key studies; a review of policy recommendations from other organizations; and committee members' expertise in teratology, embryology, medical genetics and public policy. Recommendations were formulated following discussion among the committee members. These guidelines are the consensus of the committee and have been approved by the CCMG Board.

The committee believes that the primary prevention of NTDs is preferable to surgical or medical treatment of NTDs or to prenatal detection with the option of abortion.

Findings

Recent studies have provided strong scientific evidence that maternal periconceptional use of folic acid significantly reduces the risk of NTD recurrence for couples with a child who has an NTD.[13–17] The British Medical Research Council (MRC) Vitamin Study, a randomized double-blind clinical trial involving 1195 completed pregnancies in high-risk women from 33 centres, investigated the effect of a folic acid supplement of 0.4 mg/d and other vitamin supplementation in the prevention of NTDs.[17] The study showed 72% fewer cases of NTDs among the offspring of women who had received the folic acid than among those of the women in the control group (relative risk [RR] 0.28, 95% confidence interval [CI] 0.12 to 0.71). The recurrence rate was 3.5% in the control group and 1.0% in the group of women who received the folic acid for the first 6 weeks of pregnancy. The protective effect of folic acid supplementation was even greater when the women who stopped taking the folic acid during the first 6 weeks were excluded from the analysis; the recurrence rates were then 3.6% and 0.6% respectively (RR 0.17; 95% CI 0.05 to 0.59). The result in the group taking vitamins without folate (RR 0.80, 95% CI 0.32 to 1.72) was similar to the result in the group with no vitamin supplementation.[17]

The MRC Vitamin Study was preceded by two intervention studies showing that vitamin supplementation may be preventive. In one study 0.36 mg/d of folic acid was used [14] and in the other 4.0 mg/d.[15] Both dosages were effective in reducing the rate of recurrence of NTDs.

Previous case–control studies have demonstrated that pregnant women taking multivitamins containing folic acid are at lower risk of having children with NTDs than women not taking supplements.[18–22] One of these studies reported that equivalent amounts of dietary folic acid may be sufficient to reduce the risk.[22] In contrast, a case–control study of similar design involving women from California and Illinois demonstrated no protective effect of periconceptional vitamin supplementation.[19] The difference in results may reflect regional socioeconomic and cultural variations that lead to differences in dietary folate intake in the study populations. If this interpretation is correct, the effects of folic acid supplementation may be more apparent in regions of Canada with higher rates of occurrence of NTDs, such as Quebec and Newfoundland.

Folic acid appears to be responsible for preventing the recurrence of NTDs[17] and may also prevent their initial occurrence.[18–22] At the recommended dosages folic acid is not known to harm the fetus or pregnant woman.[17,21]

The optimal dosage of folic acid for reducing the risk of recurrence of NTDs is unknown. The dosage used in the MRC study was 4.0 mg/d,[17] whereas in other studies showing a reduction in the rate of NTD recurrence it was 0.36 to 5.0 mg/d.[13–17] The use of multivitamin supplements without adequate folate supplementation does not appear to reduce the risk of recurrence.[17,21] The dose of multivitamin preparations should not be doubled to increase folate supplementation because of the potential risk to the fetus and mother from excess vitamin A and D levels.[21]

To be effective in reducing the risk of NTDs folic acid supplementation should begin before conception and be continued for the first 10 to 12 weeks of pregnancy. Neurulation occurs in early embryogenesis, before most women are aware that they are pregnant. Closure of the neural tube is complete 26 to 28 days after conception or 5 to 6 weeks' menstrual age.

Although preliminary evidence suggests that the rate of occurrence of NTDs in all pregnancies is reduced by low-dosage supplementation of folic acid[23] it is not known whether folic acid supplementation can prevent NTD recurrence in offspring of parents with NTDs, of parents with a family history of NTDs in second- or third-degree relatives or of a father who has had a child with an NTD by a previous partner. It is not known whether folic acid supplementation will help prevent the recurrence of NTDs caused by monogenic disorders (e.g., the Meckel–Gruber syndrome and autosomal dominant spinal dysraphism), chromosomal abnormalities,

amniotic band disruptions or multiple congenital anomaly patterns (e.g., caudal regression sequence).

Infants of women with insulin-dependent diabetes mellitus have a 1% to 2% risk of NTDs.[24] It is not known whether folic acid supplementation will help prevent NTDs in these offspring. Women with folic acid deficiency because of intestinal disorders (small-intestine malabsorption or intestinal bypass) may be at increased risk of having offspring with NTDs[25] and may benefit from supplementation.

Epileptic women using certain anticonvulsants are at increased risk of having offspring with NTDs. Infants of women treated during pregnancy with valproic acid have an estimated risk of 1% to 2% for spina bifida.[26] Maternal carbamazepine intake may also be associated with a risk of 1% for spina bifida in offspring.[27] It seems prudent to determine whether epileptic women planning a pregnancy have folic acid deficiency. It is not known, however, whether folic acid supplementation would decrease the risk of NTDs in offspring of women using anticonvulsants. It may interfere with metabolism and uptake of anticonvulsants, and high dosages may therefore alter seizure frequency.

Some teratogens are suspected of causing NTDs by acting as folic acid antagonists or by being associated with inadequate folic acid availability to the embryo. Aminopterin and methotrexate cause specific multiple congenital anomaly patterns that may include NTDs[28] and are contraindicated in pregnancy. NTDs also appear to occur more frequently in association with fetal alcohol syndrome. Folic acid supplementation is not known to prevent NTDs or other teratogenic effects of alcohol on the embryos and fetuses of alcoholic women. The primary goal in such women is to avoid excessive alcohol ingestion during pregnancy.

Recommendations

Women at increased risk of having a child with an NTD should be counselled about this risk and the options available to reduce it. For all women who have had an NTD-affected offspring and are planning a pregnancy or may become pregnant folic acid supplementation, 0.8 to 5.0 mg/d, is recommended in addition to a well-balanced, nutritious diet. Treatment should begin before conception and continue for at least 10 to 12 weeks of pregnancy.

Prenatal diagnosis based on previously published Canadian guidelines[29] is available to detect NTDs in high-risk pregnancies.

Validation

These recommendations for folic acid supplementation are similar to those of the Society of Obstetricians and Gynaecologists of Canada,[30] the US Centers for Disease Control and Prevention[21,31] and the Department of Health in Britain.[32]

Previous studies have not determined the minimum effective supplementation dosage, although diets containing 0.2 mg/d folic acid do not appear to be effective.[20,22] The lower limit of 0.8 mg/d in the CCMG recommendation was selected because of the results of the Czeizel and Dudas study,[23] which demonstrated a reduction in the rate of NTDs among the infants of women at usual rather than increased risk who took folic acid supplements. The upper limit of 5.0 mg/d was selected because 5.0 mg is the dose per tablet currently available commercially.

Implementation of recommendations

Programs should be implemented to educate physicians, other health care professionals and the public about the value of folic acid supplementation in preventing NTDs. Ongoing surveillance programs should monitor the prevalence of NTDs in fetuses and newborns. Basic and clinical research into the mechanisms by which folic acid prevents NTDs should be encouraged. In addition, clinical trials are needed to determine the effectiveness of folic acid in preventing the occurrence and recurrence of NTDs.

We thank Denise Koehn for nutritional advice, David Koehn for library research and Jeanette Davidson for editorial and secretarial assistance.

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